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JOURNAL OF

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EFFECTS OF ANDROGENIC STEROIDS IN AGING INDIVIDUALS*

THOMAS H. McGAVACK, M.D., JONAS WEISSBERG, M.D. AND SIDNEY PEARSON, PH.D.

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The process of aging is one of involution, degeneration and senescence, beginning in no specific or given year of life and usually proceeding in an orderly fashion, albeit with considerable individual variation. In a sense, therefore, aging may be looked upon as an accentuation of the catabolic as contrasted with the anabolic phase of metabolism. Throughout life there is a constant adjustment between the tearing down and the building up of tissue, and the movement and utilization of materials necessary to meet the energy requirements of the body.

The androgens play a vital role in the processes concerned with anabolism. They have been shown to further the storage of nitrogen in the muscular structures of the body, and also in the protein matrix of the skeleton (1–5). For this purpose protein building blocks must be furnished; apparently the androgens cannot prepare such protein moieties. Therefore, preliminary to anabolic processes controlled by androgens, other factors, probably including the "glucocorticoid" hormones of the adrenal cortex, are necessary for the maintenance of a pool of readily available protein moieties. In the presence of androgens, the protein moieties are anabolized to form muscular and skeletal protein. The catabolism of such protein may later be initiated by circulating thyroid hormone or certain adrenocortical steroids which have a specific influence in making the protein available for energy (6). Thus, the nitrogen balance of the body, and the constant turnover of protein which is necessary for normal satisfactory muscular performance is, at least in part, a hormonally regulated activity not delegated to a single gland, but apparently requiring the balanced action of gonad, adrenal and thyroid. Furthermore, pituitary function varies, as one phase of life gives way to another. Consequently, as gonadal function decreases, changes in the hormonal activity of both the pituitary and the adrenal appear. The altered responses of the adrenal cortex seem to compensate partially for the loss of gonadal function, and an asymptomatic readjustment of the body

* Presented at the Tenth Annual Meeting of the American Geriatrics Society, New York, N. Y., May 28–30, 1953.

economy is thus effected. However, if compensatory physiologic adjustment by the adrenal cortex does not occur, metabolic disturbances develop, including a negative nitrogen balance and loss of weight. These alterations commonly accompany the process of aging (7, 8).

We have been studying the metabolic effects of four androgens in aging individuals, as part of a broader geriatric program of investigation. These studies were intended to provide comparative data concerning the usefulness of these androgens in older people.

MATERIAL AND METHODS

The androgens studied were testosterone propionate, 17-methylandrostenediol, Δ^4-3,17-androstenedione, and dihydrotestosterone (stanolone). These steroids were administered intramuscularly and orally.

The patients used in these studies were on the wards of the Research Unit of the Metropolitan Hospital. They were men and women in the older age group who could be followed for long periods of time, either because they were homeless or because they had a relatively inactive chronic disorder.

In our studies of the metabolic effects of the androgens mentioned, we measured the external balances for nitrogen, potassium, sodium and chloride, the levels of various constituents in the blood and the changes in the products of excretion. These measurements were correlated with the individual's mental and muscular efficiency by means of several static and dynamic work tests.

All patients received well balanced diets at the caloric constant of about 2,200 to 2,300, with a protein-to-carbohydrate ratio of 1 to 3. However, some daily fluctuations occurred, and the range of variation was from 1,800 to 2,400 calories. A 10 per cent sample of all the foods eaten was saved for the quantitative determination of nitrogen, potassium, sodium and chloride.

Specimens of urine were quantitatively analyzed for creatinine, uric acid, 17-ketosteroids and 11-oxycorticoids in addition to total nitrogen and electrolytes.

At periodic intervals samples of fasting blood were analyzed for nonprotein nitrogen, urea nitrogen, creatinine, uric acid, potassium, sodium, chloride, cholesterol, calcium, phosphorus, albumin and globulin.

The weights of all patients were recorded twice daily, and careful clinical observations were made daily.

Analyses of fecal nitrogen were not performed, but a daily allowance of 1 gram was made in estimating the nitrogen balance for each patient.

RESULTS

I. *Testosterone propionate*

The results obtained with testosterone propionate may be summarized as follows:

Aged individuals of both sexes who were given testosterone propionate showed positive nitrogen balance, with a moderate retention of sodium, potassium and chloride (Figs. 1A and 1B). These measurable metabolic effects were mirrored in certain clinically discernible changes, namely, a gain of weight with a subjective sense of well being, and improved muscular strength as shown by the

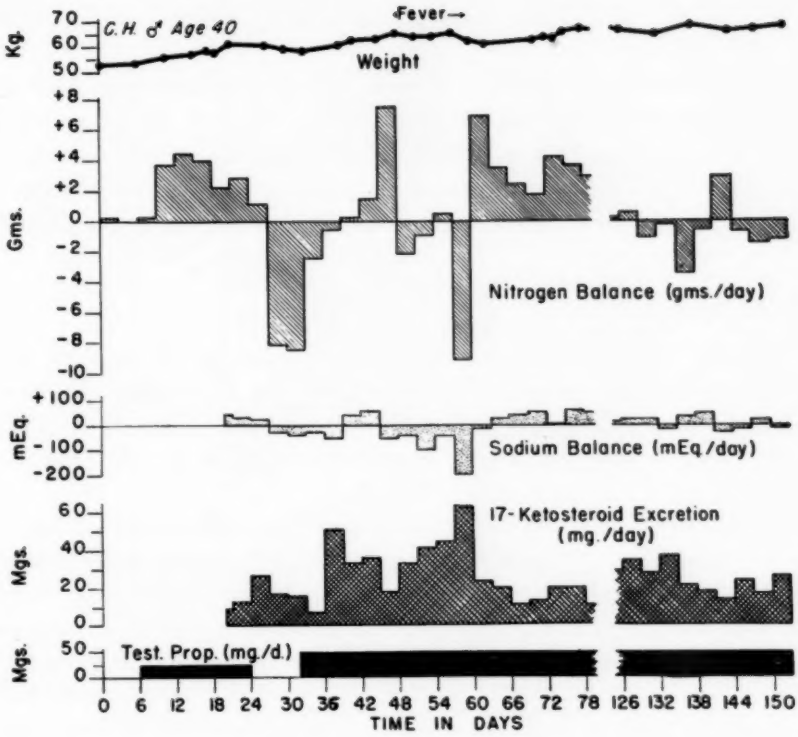

FIGURE 1A

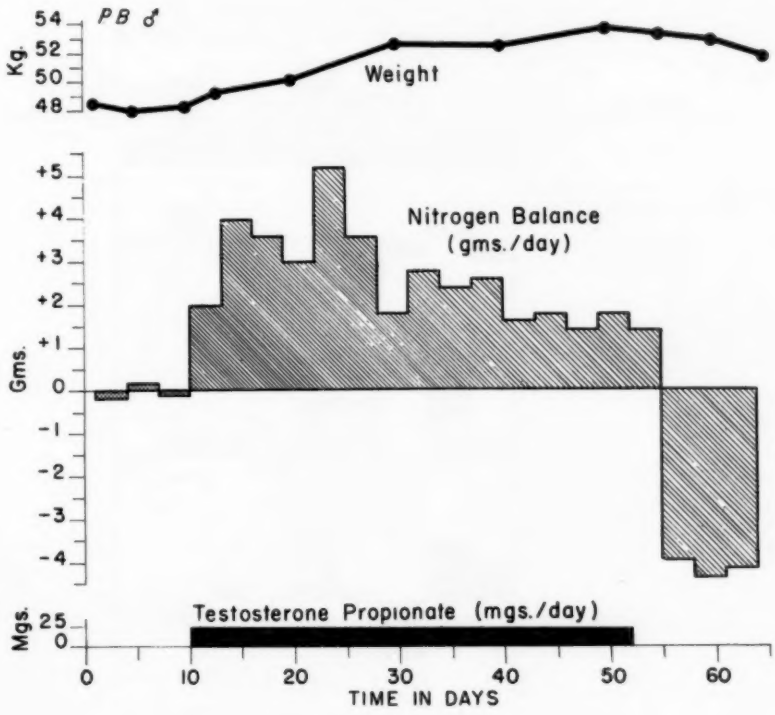

FIGURE 1B

results of static work tests and the roentgenographic demonstration of increased density of the body structures. We have observed that the presence of fever counteracts the anabolic effects of testosterone (9). Moreover, caution is necessary in the use of testosterone in older individuals with cardiovascular disease, because of the possibility that the retention of salt may precipitate congestive failure.

II. *17-Methylandrostenediol*

The metabolic effects of this steroid were studied in 15 patients, 8 females and 7 males, whose ages ranged from 52 to 88 years. The material was administered intramuscularly and orally in daily doses ranging from 25 to 500 mg. for periods of from four to eight days. The results may be summarized as follows (Figs. 2, 3 and 4):

The administration of 17-methylandrostenediol to both sexes by intramuscular injection in amounts of 100 to 500 mg. daily caused a retention of nitrogen and a gain in weight. The larger the dose, the greater was the retention of nitrogen, but each increment of dosage showed an increasingly smaller increment in effect. Orally administered methylandrostenediol in daily amounts of 50 and 100 mg. showed a definite protein anabolic activity, but it was not comparable in magnitude to that of intramuscularly administered methylandrostenediol.

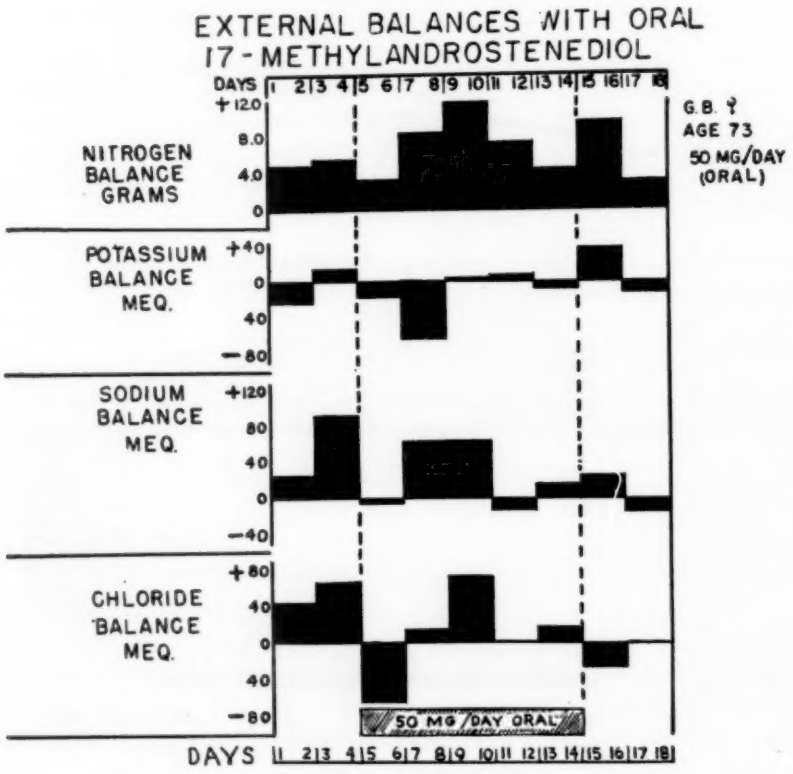

FIGURE 2

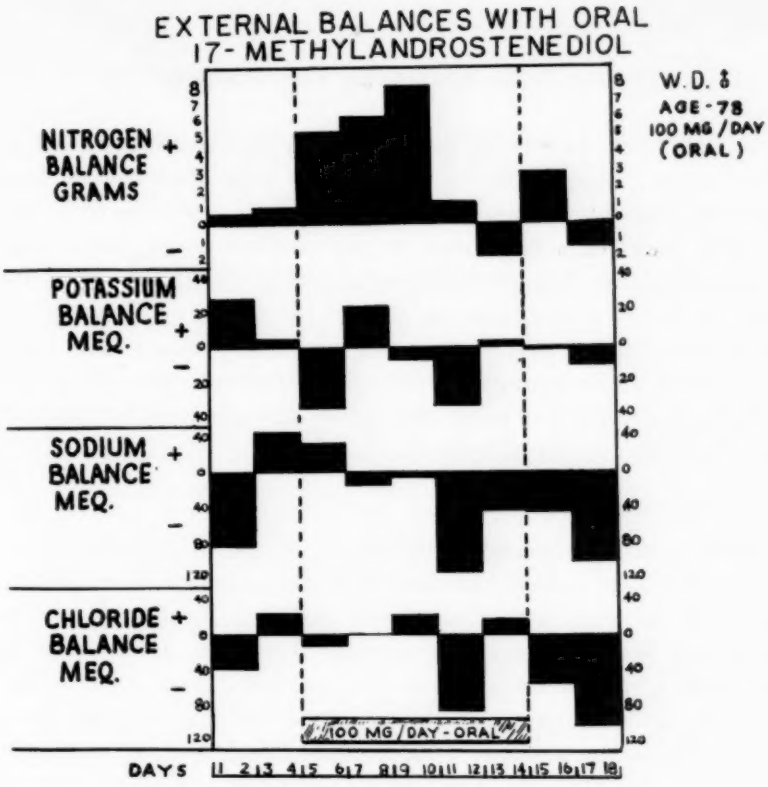
EXTERNAL BALANCES WITH ORAL
17- METHYLANDROSTENEDIOL
W.D. ♂
AGE - 78
100 MG / DAY
(ORAL)
NITROGEN BALANCE GRAMS
POTASSIUM BALANCE MEQ.
SODIUM BALANCE MEQ.
CHLORIDE BALANCE MEQ.
100 MG / DAY - ORAL
DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

FIGURE 3

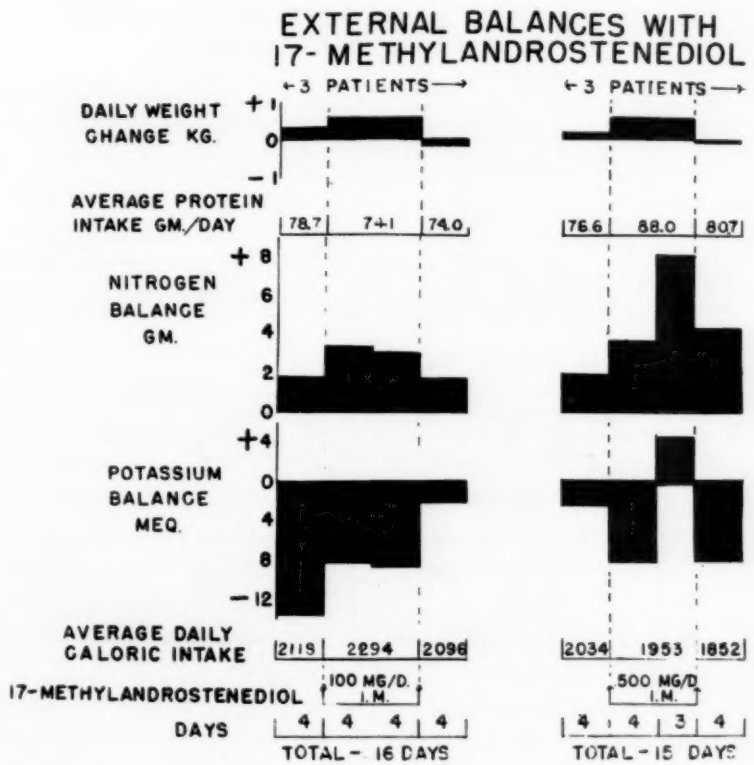

FIGURE 4

It was also found that the steroid had practically no effect on electrolyte balance when given orally, whereas the intramuscular injections caused retention of sodium and chloride. The failure to obtain electrolyte retention with oral methylandrostenediol may have been due to the smaller doses given. The general over-all results indicated that 17-methylandrostenediol had about one fourth the anabolic activity of testosterone, weight for weight. Following administration there was a sense of well being, with increased strength and vigor in both sexes. It was felt that the minimal activity of methylandrostenediol on electrolyte balance might make its use more desirable than that of testosterone in the aged individual with heart disease.

III. Δ^4-*3,17-Androstenedione*

We decided to study the metabolic effects of androstenedione as a result of some preliminary work which indicated that this compound will often improve the condition of patients with rheumatoid arthritis. Four male patients whose ages ranged from 55 to 74 years were used for the study. After a four-day period of control, during which no androstenedione was given, 3 subjects received daily for twelve days intramuscular injections of 150 mg., 300 mg., and 600 mg., respectively, of androstenedione; 1 subject, used as a control, received no drug. The therapeutic period was followed by an eight-day period of recovery.

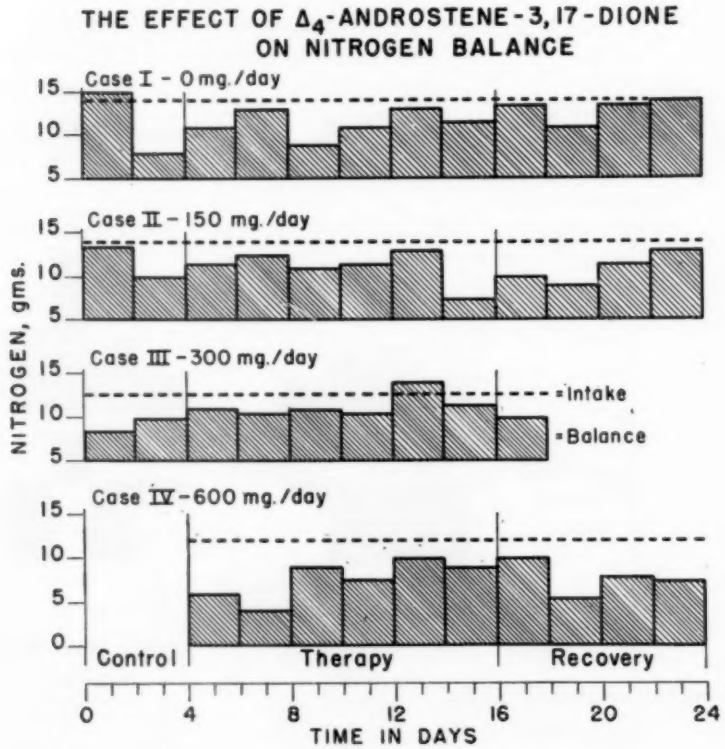

FIGURE 5A

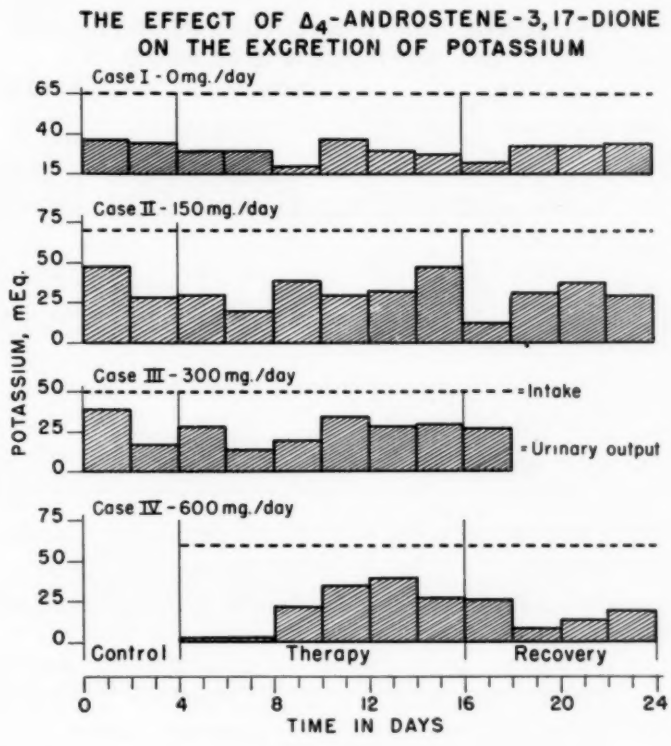

FIGURE 5B

The results of these studies (Figs. 5A and 5B) indicated that androstenedione had very little effect on nitrogen and potassium balance. The daily injections of 300 mg. and 600 mg. of androstenedione resulted in a retention of sodium and chloride. One subject showed evidence of cardiac failure as the result of salt retention. The 3 subjects who received androstenedione showed a sharply increased excretion of 17-ketosteroids, the total output in equivalents of dehydroisoandrosterone being proportional to the daily dose received.

IV. *Stanolone (dihydrotestosterone)*

Stanolone was the fourth androgen studied. This is another of the synthetic steroids with presumed androgenic properties. It has been used in the therapy of cancer of the female breast. We studied the metabolic effects of this androgen in 5 patients (3 men and 2 women) whose ages ranged from 55 to 62 years (Fig. 6). The external balances in these subjects were determined in the usual manner, during administration of from 25 to 100 milligrams of the steroid daily by intramuscular injection.

With stanolone, a moderate positive balance for nitrogen could be demonstrated (Fig. 6). Although Subject C (Fig. 6) was taking 100 mg. per day he showed considerable retention of nitrogen beginning between the fourth and sixth days, whereas Subject D (Fig. 6) showed very little variation compared with his control period. This may be the result of a difference in the condition

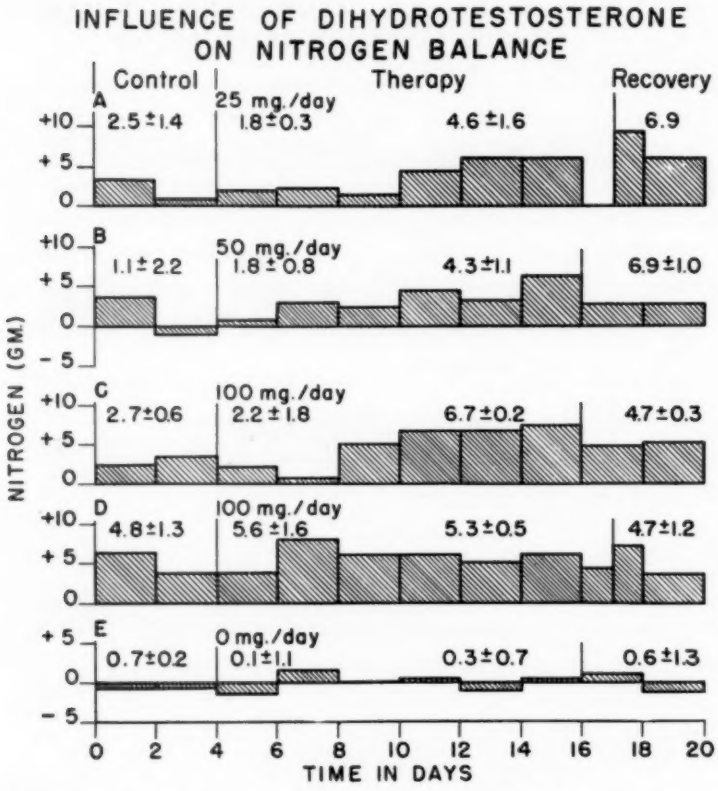

FIG. 6. Values noted on the face of each graph represent the averages for nitrogen retention. The value to the left in the therapy period refers to the first six days and the value to the right refers to the rest of the time during which steroid therapy was used.

of the two patients. Subject D was the only one who had not had at least a period of one month on the wards of the Research Unit prior to the initiation of the observations. About five days before this study was started, the subject selected was dropped. Subject D, who replaced him, had been admitted to the hospital only three days before the control period began. On careful questioning it was found that his previous intake of food had been poor. Therefore, during the control period, he showed a rather marked retention of nitrogen, which was only slightly enhanced by the use of the steroid. In none of the subjects to whom stanolone was administered were the balances for sodium, potassium and chloride essentially altered. The patients who received this steroid reported a sense of well being with improved appetite. A weight gain was also noted, with an increased capacity for muscular and mental activity.

COMMENT

As a result of the foregoing studies and of additional clinical application, a table has been constructed in which the nitrogen and salt-retaining properties of the four androgens are compared (Table 1). The values for these comparisons have not been reached by biostatistical analysis, but represent the trends we

TABLE 1

Comparison of Anabolic Activity of 4 Androgens

Steroid	Relative retention*	
	Nitrogen	Salt
Testosterone	100	100
Methylandrostenediol	25	15
Dihydrotestosterone	35	15
Androstenedione	0	20

* The activity of testosterone has been arbitrarily placed at 100 and the potency of the other preparations has been expressed in relation to this figure. This comparison is not accurate biostatistically, but is used merely to suggest the relative trends of activity.

have observed in the work at the Research Unit. In such a comparison it is obviously difficult to include all the factors which actually enter into a proper appraisal of any therapeutic agent. For instance, on casual inspection of our figures, particularly Figures 4 and 6, one gains the impression that methylandrostenediol is a more active agent for the retaining of nitrogen than is stanolone (dihydrotestosterone). On closer inspection, it is seen that the data for stanolone during the test period have been divided into two separate groups: 1) for the first through the sixth days, and 2) for the seventh through the twelfth or thirteenth days. This separation was made because in no instance was any striking difference in nitrogen balance displayed until the sixth or seventh day. During the latter part of the test period, a very positive nitrogen-retaining effect was present. This effect, once begun, was clearly greater than that achieved on the average in patients who received methylandrostenediol. Furthermore, effects from stanolone were better sustained in the recovery phase than were those from methylandrostenediol. For this reason it was given a higher rating than methylandrostenediol, as regards the retention of nitrogen.

SUMMARY

Observations are presented on the metabolic effects of four androgens in aging individuals. Testosterone propionate, 17-methylandrostenediol and stanolone (dihydrotestosterone) are anabolic in their actions, as judged by their ability to cause retention of nitrogen and potassium, and to some extent, of sodium and chloride. Testosterone propionate possesses the greatest activity. Because the retention of sodium and chloride is less following 17-methylandrostenediol than following testosterone, it may be that this drug is preferable as an anabolic agent in patients who have cardiovascular disease with present or impending congestive failure. The androgen Δ^4-3,17-androstenedione had no effect on nitrogen or potassium balance but did cause some retention of sodium and chloride. Each of the four androgens gave the patients a sense of well being with an increase in muscular and mental activity.

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PERIPHERAL VASCULAR DISEASE IN GERIATRICS

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Arterioslcerotic vascular changes associated with vascular insufficiency, particularly in the lower extremities, are an ever present problem in our aging patient. Although the older individual is heir to many of the vascular disturbances present in his younger brethren, the gradual occlusion of the arterial circulation, secondary to arteriosclerotic processes, still is the number one vascular problem in this age group. The slow process of diminished blood flow in the lower extremities may go on for months or years before the patient becomes aware of its existence. Only when the metabolic demands of the tissues exceed the supply of arterial blood does the patient seek medical attention. Symptoms of vascular insufficiency are manifested either by functional disturbances, such as intermittent claudication, or trophic changes due to inadequate circulation in the superficial tissues.

It is well to remember that calcific changes shown by radiography in the large and medium sized arteries of the lower extremities are not a primary cause for signs and symptoms in this disorder. Only when the blood flow in the minute vessels, the arterioles and capillaries, is inadequate do the sign and symptoms of peripheral vascular disease become prominent. In many patients with marked radiographic changes suggesting extensive calcification of the larger arteries sufficient collateral circulation develops to insure adequate blood flow in the minute vessels. On the other hand, patients with only minimal radiographic changes of arteriosclerotic vascular disease in their medium or larger blood vessels may show considerable change in the smaller arteries and arterioles which cause functional or organic disorder.

MANAGEMENT

No one can question the value of physical modalities in the management of peripheral vascular disease in the elderly patient. The multiplicity of physical measures employed, however, in this group of diseases suggests that no single modality for any condition affecting the peripheral circulation is curative in itself. During the past decade attention therefore has been directed toward the integrated over-all care of the patient, using physical measures as an adjunct to other medical and surgical procedures. We have three primary objectives in the management of the patient with peripheral vascular disease. First, the prevention of tissue necrosis by alleviating the disproportion between the demands

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of tissue metabolism and the diminished blood supply. Second, maintaining viability in tissues not already irreversibly damaged. Third, rehabilitating the patient as a whole.

Prevention of tissue destruction

Although arteriosclerotic vascular disease is fundamentally an organic change in the vascular lumen, it is well known that varying degrees of vasoconstriction are usually present. It would therefore be a fundamental principle to instruct the patient in regard to any general factors which cause increased vasoconstriction. Reflex vasoconstriction due to even slight chilling, emotional stress or prolonged standing, must be avoided in this group of patients. The absolute avoidance of smoking should also be stressed. Likewise, any physical agent which may increase the local metabolic demands of tissue beyond the capacity of the diseased peripheral circulation should be avoided. In this regard irreparable damage can be done to the tissue and necrosis and gangrene can result.

All forms of local heat, whether one uses diathermy, luminous heat, or conductive heating, are definitely contraindicated in the presence of organic vascular insufficiency. Others forms of reflex vasodilatation should be employed. The danger of applying heat locally to a relatively ischemic extremity cannot be stressed too vigorously, particularly to nurses and attendants. The patient should be advised to avoid the local use of hot wet soaks or electrically heated pads, if there is any small area of infection present. In most instances we rely primarily on the avoidance of chilling and maintaining optimum skin temperature by having the patient wear warm socks and clothing. Where increased vasodilatation is desired, reflex vasodilatation may be obtained by local heat applied in any one of several methods to the trunk, abdomen, or uninvolved extremities. Since the objective in treating the patient with peripheral vascular disease is the prevention of tissue destruction, it would appear that the proper instruction of the patient in details of foot hygiene, shoe fitting and simple methods of reflex vasodilatation are probably more effective for most elderly patients than any mechanical apparatus, which of necessity can be used only over a limited period of time and frequently at great expense.

Maintenance of viability

Although excessive walking or standing is contraindicated in the elderly patient with peripheral vascular disease, one should encourage active non-weight bearing exercises. Bed exercises, either of the Buerger-Allen type or simple muscle setting exercises, hip-knee flexion, ankle curling, and toe flexion and extension, particularly for the patient who is only semi-ambulatory, are all excellent methods for maintaining optimum blood flow to the involved extremities, without any inherent dangers. Mechanical contrivances, such as the Pavex boot, or intermittent venous occluding pressure, have their place in the management of peripheral vascular disease, but are believed to be less useful than was previously thought. Any mechanical procedure which can be used only for thirty minutes to an hour once or twice daily is far less important than the patient's regimen

during the remaining twenty-three hours each day. In the past few years the Saunders oscillating bed has been widely employed with encouraging success in patients with impending gangrene who fail to respond to other conservative methods. In essence, the oscillating bed appears to be a continuous type of Buerger-Allen postural exercise which can be carried out over a period of many hours daily.

Rehabilitation of the patient

In general, the interest of most physiatrists today is turning from emphasis on mechanical apparatus as a cure or prophylaxis in the management of peripheral vascular disease, toward a total rehabilitation of the patient, emphasizing the simpler, more conservative measures of treatment. As mentioned previously, emotional stress and strain and worry over the future may have a very deleterious effect by producing increased and prolonged vasoconstriction. We feel that it is important to reorient the patient, relieve his apprehension and assure him that under a good, conservative regimen the probability of serious sequelae is made less likely. When vascular disturbances have progressed to the point of gangrene, amputation, either below the knee, or as more frequently advised, above the knee, is indicated. It is well for the older patient facing amputation to realize that with modern prosthetic techniques and training he can satisfactorily learn to use an artificial limb. We have found the only criterion for determining whether or not a patient will be able to employ an artificial limb satisfactorily is his ability to ambulate with the use of crutches following amputation. Rather than set any specific age as the upper limit for obtaining prostheses for the older amputee, it has been our experience that any patient who satisfactorily can ambulate using two crutches following amputation can use a properly fitted prosthesis. It is unwise to fit the older patient with a prosthesis if he is unable to ambulate satisfactorily with the use of crutches.

Today the treatment of peripheral vascular disease in the older patient has become increasingly efficient because of the cooperation between the internist, the surgeon and the physiatrist. Circulatory deficiencies are recognized earlier and treatment is begun before irreversible damage leads to loss of an extremity. The fundamental framework of treatment rests on a good physiologic basis. In judging any method of therapy in this group of patients we should be guided by its simplicity and by objective evidence of its efficiency, its physiologic soundness, and the permanence of response. It is because of these general principles, rather than the employment of any specific physical gadget or modality, that the prognosis in the patient with peripheral vascular disease is better today than a decade ago.

MANAGEMENT OF DIFFUSE OBSTRUCTIVE PULMONARY EMPHYSEMA

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The management of degenerative diseases has become a problem of increasing magnitude to practicing physicians. This problem arises in part as a consequence of more successful control of acute diseases. Diffuse obstructive pulmonary emphysema may well be classified in the group of so-called degenerative diseases. Although the chronic form may occur in patients of almost any age, it is primarily a disease of men in and beyond the fifth decade of life. Why this condition occurs chiefly in middle-aged and elderly men is not known, and exact knowledge of its pathogenesis is limited.

Because of the incomplete understanding of this process and its chronic progressive nature, therapeutic management has posed a serious problem. The occurrence of chronic or recurrent respiratory affections, such as tuberculosis, certain types of pneumoconiosis and nonspecific bronchitis, is thought to be related to an increased incidence of pulmonary emphysema. The successful treatment of tuberculosis and other specific bronchopulmonary infections may lead to survival of patients who will likely be predisposed to a greater incidence of pulmonary emphysema in the future. The increasing average age of the general population gives another indication that there are now greater numbers of persons in the age groups in which pulmonary emphysema is a common problem. Only further basic and clinical investigation will lead to more successful management of patients who have pulmonary emphysema. However, for the present, the clinician is faced with the problem of treating patients who have pulmonary insufficiency in the light of current knowledge.

EVALUATION OF THE PROBLEM

Numerous methods of treatment for patients who have pulmonary emphysema have been advocated, thus suggesting that no one method has been highly successful. Because of these numerous possible approaches, it becomes particularly important to have as complete an understanding of the patient's disability as is possible before a program of management is begun. Some of the traditionally accepted signs are not necessarily indicative of diffuse obstructive emphysema, and may lead to a false positive diagnosis. Conversely, some of the classic findings may be absent in the presence of emphysema. A careful appraisal of all evidence is especially important in making a diagnosis. Diffuse obstructive pulmonary emphysema has several cardinal features that may be demonstrated by the history, by physical findings in the examining room, by roentgenologic studies and by the use of simple spirometry.

The commonest chief symptom is dyspnea; probably all patients who have this

* The Mayo Foundation is a part of the Graduate School of the University of Minnesota

disorder experience some degree of exertional dyspnea. A diagnosis of clinical diffuse pulmonary emphysema is on uncertain ground in the absence of this symptom. Cough, expectoration and wheezing respiration usually occurring shortly after arising or with exertion also may contribute to the patient's discomfort. Chronic asthmatic bronchitis, or so-called endogenous asthma, is frequently associated with diffuse obstructive emphysema and probably contributes to its pathogenesis.

Obstruction to the expiratory flow of air is a consistent finding. Prolongation of the expiratory breath sounds and even wheezing may indicate this abnormality. However, these changes may not be observed during normal resting ventilation but only while the patient is breathing deeply and rapidly, as when maximal breathing capacity is used or during a forced maximal expiratory effort. Breath sounds may be diminished, with associated hyper-resonance. Thoracic expansion may or may not be reduced and is not a constant and reliable measure of pulmonary function. The thorax is not always "barrel-shaped" in patients who have emphysema; furthermore, the presence of an increase in the anteroposterior diameter of the thorax is not pathognomonic of diffuse obstructive pulmonary emphysema. Clinical cyanosis is present only in far-advanced stages of the disease, at which time other and more specifically diagnostic signs are already apparent.

Obstruction of the airway may be demonstrated fluoroscopically by the extremely slow and incomplete reduction in radiolucency of the pulmonary fields when the patient makes a forced maximal expiration. This abnormality may be generalized, as in diffuse obstructive emphysema, or localized, as in emphysema secondary to local bronchial disease, such as tuberculous stricture. A roentgenogram of the thorax taken at the end of a single, full inspiration is not always sufficient for the accurate roentgenologic diagnosis of emphysema. Inspiration-expiration roentgenograms or those taken with the patient in the lateral decubitus position give information similar to that provided by fluoroscopy. Little diaphragmatic excursion is evident at the extremes of the respiratory cycle. In lateral-decubitus roentgenograms of patients who have emphysema, the dependent leaf of the diaphragm does not usually move as far cephalad as it does in normal persons. Spirometric tracings show abnormally slow emptying of the lungs in emphysema. Reduction of maximal breathing capacity out of proportion to reduction in vital capacity further indicates obstruction to the flow of gas. The absolute increase in residual volume, another consistent feature of diffuse obstructive emphysema, may be specifically measured only by indirect methods requiring analysis of gases. Detection of impairment in intrapulmonary mixing of gas similarly requires special apparatus for analysis of gases. When arterial oxygen desaturation occurs, secondary polycythemia or cor pulmonale or both may appear and require special management (1).

TREATMENT

The treatment of chronic diffuse obstructive emphysema may be classified into three general categories, namely medical, physical and surgical.

Medical.—This type of treatment includes numerous procedures, most of which are relatively simple. Any patient who has dyspnea, wheezing or cough should avoid respiratory irritants. One of the most common of these is tobacco smoke; such patients should abstain from smoking. Farmers often note a pronounced increase in symptoms when around dusty places, such as the barn, or during harvesting activities. A change in occupation or location may be required, depending on the severity of symptoms. Cold, damp weather frequently aggravates symptoms. However, no permanent decision regarding a change in climate should be made without previous temporary clinical trial for a period of weeks or months. Activity that greatly aggravates dyspnea and wheezing or cough should be avoided, but marked restriction of activity is inadvisable, since it may result in general muscular weakness and wasting.

The use of aerosolized bronchodilators is one of the most consistent methods of improving symptoms. In many instances, measurement of vital capacity and maximal breathing capacity shows a beneficial effect that lasts several hours after administration, for example, of an aerosol of 0.5 ml. of a solution of isopropylarterenol (1:200) with equal parts of water. A hand bulb may be used to produce the aerosol in the nebulizer. However, use of an oxygen tank as a source of pressure, with an indicated flow of about 4 liters per minute, requires less effort by the patient during a period of treatment lasting ten minutes or more, and also increases arterial oxygen tension. Many patients with emphysema have severe symptoms early in the morning on arising; washing and shaving may produce an unusual degree of dyspnea. The use of a bronchodilating aerosol immediately after the patient has arisen frequently improves these early-morning difficulties.

Aminophylline administered orally, parenterally or by suppository may help in some cases. Oral use of ephedrine in combination with a barbiturate also may benefit some patients, especially if asthmatic bronchitis is prominent. Expectorants containing iodides often are helpful if cough and thick tenacious sputum are troublesome. However, some patients cough excessively and produce little other than the normal mucus lining the tracheobronchial tree. These patients should be advised to suppress the cough reflex, since they gain almost nothing by repeated coughing. It appears likely that cough may play an important role in the progression of diffuse obstructive emphysema (2). Codeine is of little help in managing chronic cough.

Chronic infection is often the cause of chronic cough and many patients who have pulmonary emphysema are subject to recurrent and prolonged respiratory infections. Expectoration of mucopurulent material usually accompanies infections of the tracheobronchial tree and is an indication for use of antibiotics (3). The results of cultures of sputum, obtained before treatment is begun, aid in the choice of an appropriate antibiotic or combination of antibiotics. Frequently, however, cultures show only the usual flora, the natural inhabitants of the upper part of the respiratory tract. In these cases, a program of intermittent use of varied antibiotics may aid in the reduction of cough and mucopurulent secretions without predisposing to overgrowth of certain resistant strains of bacteria or

fungi. A typical program includes rotation of periods during which drugs are given and periods during which no antibiotic is used. For example, the patient may use a drug for five consecutive days during one month, followed a month later by a five-day course of treatment with another drug having a different mode of antibacterial action. Penicillin given by aerosol, by injection, or orally, may be used first, and oxytetracycline (Terramycin) or chlortetracycline hydrochloride (Aureomycin) may be given orally for another short period the next month. Each subsequent month the drugs may be used alternately. If purulent bronchitis or frank bronchiectasis is associated with emphysema, such a medical program often is helpful; in addition, postural drainage might be indicated.

As mentioned previously, chronic pulmonary emphysema is occasionally accompanied by polycythemia and cor pulmonale with congestive cardiac failure; intermittent or persistent arterial hypoxemia appears to be an important factor in these changes (1). Improvement in arterial oxygen saturation, if this could be achieved, should prevent or delay the development of such complications. The employment of methods to improve pulmonary ventilation at times will improve hypoxemia. When polycythemia does occur, phlebotomy is often helpful. In the rare cases in which secondary polycythemia and hypervolemia are so persistent as to require phlebotomy at least once a month, radioactive phosphorus may be employed to suppress the overactivity of the bone marrow. Digitalis, diuretics and restriction of salt in the diet may be required to relieve the edema of cor pulmonale. Use of diuretics may precipitate metabolic acidosis because of renal loss of sodium or through the accumulation of chloride, as with administration of ammonium chloride. If the presence of respiratory acidosis is suspected, diuretics should be used with caution.

Physical.—Numerous physical methods have been proposed in the treatment of pulmonary emphysema. They have been directed chiefly at elevation of the position of the diaphragm at the end of expiration.

Use of abdominal belts has been prescribed and special emphysema belts are manufactured by several companies making orthopedic garments. Artificial pneumoperitoneum has been reported to be of benefit in some cases when used either alone or in conjunction with an abdominal belt (4). The general applicability of pneumoperitoneum, however, has not yet been established.

Breathing exercises are prescribed, not only to elevate the level of the diaphragm at the end of expiration but to re-educate the muscles used in respiration and to obtain better ventilation with less effort through muscular co-ordination (5). Many patients who have pulmonary emphysema unconsciously place the chief burden of ventilation on the upper thoracic and intercostal muscles, often calling into play the accessory muscles of respiration in the neck. The use of abdominal breathing is an important feature of exercises in emphysema. Since these patients carry out the respiratory cycle with the thorax already in an inspiratory position, emphasis is placed on slow but forceful and more nearly complete emptying of the lungs with expiration. Breathing exercises present a simple method of treatment that the patient may learn with careful professional supervision.

Use of intermittent positive-pressure breathing (IPPB) instruments, into which are introduced aerosolized bronchodilators, with oxygen tanks as a source of pressure, has been recommended in the treatment of pulmonary emphysema (6, 7). The value of aerosolized bronchodilators alone in these patients already has been discussed. Whether or not the addition of intermittent positive-pressure breathing adds materially to the effects of treatment in a majority of patients is debatable. Fowler, Helmholz and Miller (8) found that the use of intermittent positive pressure gave no appreciable added benefit to the use of aerosolized bronchodilators alone in ambulatory patients with emphysema. Nevertheless, there are probably numerous clinical situations in which intermittent positive-pressure breathing is of distinct value. The problem of respiratory depression and acute retention of carbon dioxide in chronically hypoxemic patients as the result of oxygen therapy presents one of these situations. The respiratory drive has been greatly depressed in these patients and an artificial method of improving pulmonary ventilation would appear advisable.

Additional measures in the management of acute retention of carbon dioxide or oxygen poisoning might be mentioned. This complication may occur in any instance of chronic pulmonary insufficiency in which hypoxemia is present, with retention of carbon dioxide in the blood. When these patients are exposed to high concentrations of oxygen, the minute ventilation may decrease greatly. Although the patient's color may improve, he becomes dull mentally; muscular twitching may appear, followed by coma and, in some instances, death. Numerous theories of pathogenesis have been proposed (9). However, decreased ventilation and acute retention of carbon dioxide appear to be inherent features in the syndrome. Methods directed at maintaining fairly normal ventilation during oxygen therapy have been helpful in preventing changes in the central nervous system. The use of slowly increasing amounts of oxygen by nasal catheter (10) or by mechanical respirators has been effective (11). The Drinker type of respirator does not adjust itself to the subject's natural respiratory cycle; thus a patient who is breathing voluntarily may fight the machine. However, with the various types of valves available to allow intermittent positive-pressure breathing, the rate of delivery of oxygen during inspiration is initiated by the patient's respiratory rate. This feature, plus the ease with which the valves may be transported and the need of only a tank of oxygen as a driving source, is an advantage of the IPPB apparatus over the Drinker respirator. The pressure attained during inspiration with IPPB may be regulated and is usually set at, or below the level for 20 cm. of water.

Surgical.—Numerous surgical procedures have been devised to improve pulmonary function in certain cases of pulmonary emphysema. These are directed at collapse or removal of large emphysematous bullae or pneumatoceles that might encroach on surrounding normal pulmonary parenchyma (12, 13). It is the exceptional case, however, in which a large bleb occurs in the absence of a diffuse emphysematous process. Excision of such blebs is preferable if the patient is a satisfactory surgical candidate. However, if operation appears to be of great risk to the patient, collapse of the air-containing cyst might be achieved by Monaldi's (continuous suction) drainage.

Abbott and associates (14), who have studied the problem of pulmonary emphysema, advocated resection of large pulmonary bullae in association with various types of resection of intrathoracic autonomic nerves in selected cases.

Recurrent spontaneous pneumothorax occurs in occasional cases. Exploratory thoracotomy may be indicated in order to effect closure of a bronchopleural fistula resulting from repeated rupture of a subpleural air-containing cyst. Recurrent spontaneous pneumothorax, however, is usually seen in otherwise healthy young adults who have one or several isolated subpleural blebs in the absence of diffuse emphysema. Intrapleural poudrage also has been employed in treatment (15).

COMMENT

The general approach to management of the patient who has diffuse obstructive pulmonary emphysema warrants special comment. Even the emotionally well-adjusted person finds it difficult to face the future with a chronic progressive illness. Although the patient should be told in detail about the nature of his illness and the lack of a perfect method of cure, it would appear wise to maintain an air of optimism. He should be told that there are numerous methods of improving his difficulties, although the treatment may not lead to cure. The best combination of these methods to suit the individual patient usually can be found. Continuous knowledge on the part of the patient that there is always something else that may be tried, and conscientious enthusiasm on the part of the physician, may go a long way in potentiating the results of the somewhat empirical methods currently available for the treatment of the disease.

SUMMARY

Current knowledge regarding the cause and pathogenesis of diffuse obstructive pulmonary emphysema is limited. Therefore, treatment comprises a number of empirical measures of varying merit. More specific and successful therapeutic regimens will likely accompany greater understanding of the basic disease process. Nevertheless, the physician is faced with the problem of managing these patients who have chronic progressive pulmonary disease, in the light of present knowledge. The complexity of the program of treatment should match the degree and progress of each patient's disability. Medical, physical and surgical measures of treatment have been advocated. The wide variety of proposed therapeutic measures allows the physician to seek the best combination for controlling, at least temporarily, the progress of the disease. Many of the proposed methods of treatment have been outlined briefly.

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MAINTENANCE OF GOOD HEALTH IN OLDER PEOPLE

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Active aged individuals have been appearing more and more frequently in the general practice of medicine. Such persons are rarely truly well, as only the smallest minority report for routine examination if they are actually "blooming." More commonly such patients are not seriously affected by disease, but have mild complaints referable to one or more systems. Their difficulties are more a lack of well-being than actual sickness.

When the older patient suffers severe skeletal, neurologic, cardiovascular, or neoplastic disease, he is treated accordingly. Other milder complaints often plague him, however, and are presented to the physician as a significant problem in therapeutics. These conditions present a challenge in health maintenance even greater than in younger persons, as often the symptomatology is far less precise. Anorexia, flatulence, various aches and pains, insomnia, mild cardiac decompensation problems, fatigue and headache, and inadequate grasp of the realities of modern living are typical complaints and may appear in any combination. These symptoms are increasing in frequency generally because individuals are now being kept alive who in an earlier day would have succumbed to specific disease. Moreover such mild symptoms may also distress aged persons suffering more serious illness. For instance, the arthritic may also have mild cardiac decompensation, and the terminal cancer patient may have tension headache or mild pruritus.

It should not be presumed that the mild symptoms referred to here are necessarily trivial. Some may have a profound effect, not only on the well-being but actually on the life of the oldster. Anorexia or fatigue, for example, may be a surface manifestation of a very serious pathologic condition that may be undetectable by objective means; however, the delicate balance in a geriatric patient may be fatally disturbed unless the symptom, and presumably also the underlying disease, is rapidly brought under control.

The supervision of such problems may demand a great deal of the physician, both as to diagnosis and treatment, in accord with the philosophy of medical practice that the utmost be done for each complaint in each patient. Each separate symptom must be considered on its own merits, and may or may not be related to other complaints or findings. Thus, not uncommonly, regularization of a fibrillating pulse may increase general well-being surprisingly, or elimination of minor gastrointestinal distress may ease cardiac or arthritic symptoms. Treatment may be directed at each involved system separately, or mild sedatives or such central nervous system stimulants as dextro-amphetamine, or various com-

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binations of these, may be utilized. Many investigators in the past have used a variety of substances, often actually or theoretically related to sex organs, and have reported considerable success; their results, however, could not be duplicated with any great degree of dependability. Nevertheless changes in the metabolism of the sex hormones and related steroids seem definitely related to the aging process (1).

Recent investigations indicate that the aging process is accompanied by inadequate metabolism and utilization of steroids, and recent therapy has been oriented in this direction. Biskind *et al.* (2, 3) demonstrated that lack of the vitamin B complex led to inadequate metabolism of estrogen and estrone in the liver. Pollak (4) reported that lipotropic factors seem to have a beneficial effect on the utilization of steroids (4). It is the impression of investigators in this field that steroids, vitamin B complex, and lipotropic factors act synergistically, seeming to "save" or energize each other, or to act as mutual catalysts enhancing one another. Thus they seem to have a significant value in problems relating to atherosclerosis and arteriosclerosis (5–10). The latest contribution in this field comes from C. B. Anfinsen, of the National Heart Institute, Bethesda, Md. In a paper as yet unpublished, but presented at the December 1953 meeting of the American Pharmaceutical Manufacturers Association, he pointed out the relationship between steroid hormones and lipotropic factors, particularly with regard to the treatment of atherosclerosis and related conditions.

With this general concept in mind, we have used a combination of steroid, lipotropic and vitamin B complex factors in private practice during the past year (Table 1). The combination has been administered in the form of a mixture of two trade products, which we have designated Product T and Product V.[1] Both contain the lipotropic factors inositol (50 mg. per cc.), choline chloride (10 mg.) and *d-l*-methionine (10 mg.), and the B-complex factors thiamine hydrochloride (10 mg.), riboflavin (2 mg.) pyridoxine hydrochloride (5 mg.), and niacinamide (40 mg.). In addition, Product T contains 12.5 mg. of testosterone and Product V contains 1 mg. (10,000 I.U.) of natural estrogen. These mixtures are best administered together—0.5 cc. of each mixed fresh in the syringe just before injection. They have been used in a series of 22 patients, 5 male and 17 female, ranging in age from 58 to 88 years. Admittedly some of these patients are below the age considered to be geriatric, but it is felt that they belong in this group because of the nature of their symptoms and their state of mind.

Many of these mild symptoms would probably respond to specific therapy, such as digitalization or sedation, but the interesting fact is that they seem to respond as well to a less specific routine.

Each course of therapy was started with an injection three times a week for two weeks, and continued at a maintenance level of an injection every five to fourteen days. In each case, after maintenance dosage had been determined, placebo injections were substituted from one to three weeks, in order to eliminate the suggestion factor as much as is possible in a private practice. Following the

[1] Product T is Testramone; Product V is Vitramone. Both are manufactured by Harvey Laboratories, Inc., Philadelphia, Pa.

TABLE 1

Patient	Sex	Age (yrs.)	Complaints*	Duration of therapy (wks.)	Result	Comment	Present activity
A. A.	F	63	Fa Dz H De	24	Good	Continuing weekly	Housewife
J. A.	F	62	N I	4	Good	Moved away	Housewife
I. B.	M	83	De Fa P	6	Good	Continuing twice weekly	Active in a nursing home
H. B.	F	60	N I	6	Good	Moved away	Housewife
B. B.	F	78	W A I R	4	Fair	Refused further care because of painful injection	Inactive in a nursing home
G. C.	F	62	N A	12	Good	Continuing weekly	Housewife
K. C.	F	85	Fa De A P	24	Good	Continuing weekly	Active around home
A. C.	F	63	Fa De	6	Good	Death from cerebral vascular accident	
M. D.	F	63	N F	17	Good	Continuing monthly	Shop clerk
F. D.	F	76	De F	8	Good	Moved away	Housewife
I. G.	M	63	De	12	Good	Continuing weekly	Supervises own shop
M. H.	F	59	Dg W H I	22	Good	Continuing semimonthly	Housewife
L. H.	F	75	Fa De P	6	Poor (P improved)	Severe osteoarthritis	Semi-active at home
J. K.	F	60	Fa W N	22	Good	Testramone only (on combination, once had severe metrorrhagia)	Housewife
G. K.	M	58	C N	22	Fair	Better relief than with testosterone	Factory worker
S. K.	M	86	Fa A Dz P	16	Good	Continuing weekly	Moderately active at home
B. K.	F	76	A	8	Poor	Severe osteoarthritis	Inactive in nursing home
B. M.	M	60	Fa De	10	Good	Continuing monthly	Part-time work
A. R.	F	63	R Fa N P	8	Good	Continuing weekly	Moderately active at home
M. R.	F	81	A Dg N W H	22	Good	Severe chronic colitis; continuing semimonthly	Housewife
M. V.	F	88	De Fa A	22	Good	Continuing weekly	Housewife
E. W.	F	65	N I Dg	10	Good	Continuing irregularly 1–4 wks.	Seamstress

*A—Anorexia. C—Male climacteric. De—Mild cardiac decompensation. Dg—Mild digestive complaints. Dz—Dizziness. F—Flatulence. Fa—Fatigue. H—Headache, I—Insomnia. N—Nervousness. P—Pruritus (mild). R—Inability to adjust to reality. W—Weakness

placebo injections, in all but 2 patients there was an appreciable decrease in the sense of well-being, which quickly returned with re-administration of the products T and V. The 2 patients who experienced no drop in the sense of well-being have been maintained in this condition under placebo medication, and are presently quite dependent on administration of sterile water.

In occasional cases, during the period from about the third to the tenth injection, there occurred a moderate ankle edema. At first this was treated by combining a mercurial diuretic (Thiomerin or Mercuhydrin) with the injection, in doses of 0.5 to 1.0 cc., and more recently by oral administration of 1 to 3 Neohydrin tablets daily. Usually after about the eighth or tenth injection the ankle edema disappears completely and does not recur.

It must be admitted that all the improvement reported in this series is subjective, and that such subjective changes are always difficult to measure, particularly in the aged. Nevertheless the obvious change in the appearance of the patients and reduction of complaints must be given a certain credence, as no known objective test is available to evaluate the concept of general good health.

SUMMARY

1. In the care of the active aged it is important to recognize that although these individuals consider themselves generally healthy, they may enjoy less than the best possible health.

2. Between the seriously ill and those who are in excellent condition is a significant group of the elderly who have only minor symptoms. Many of these minor symptoms respond not only to specific therapy, but also to a combination of nonspecific agents.

3. A combination of such agents, containing androgen and estrogen, lipotropic factors and vitamin B complex was used in a small series of cases in private practice. The results are reported.

4. In 18 of 22 patients there was significant subjective improvement; in 2, moderate improvement; and in 2, no benefit.

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ORAL METRAZOL THERAPY IN PSYCHOTIC SENILE AND ARTERIOSCLEROTIC PATIENTS

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The population of mental state hospitals is growing increasingly older, much more so than the population at large. In Springfield State Hospital, Sykesville, Maryland, which accommodates about half of all white patients in Maryland's State mental hospitals, more than 25 per cent are 65 years of age or older. According to the 1950 census, the proportion of white people over 64 years of age in the State of Maryland is approximately 7.5 per cent of the total population. Thus, comparatively speaking, in our hospital there are more than three times as many "old people" (over 64) than in the general white population of Maryland.

A great many of the old people in state hospitals are psychotic senile and arteriosclerotic patients. Mentation and behavior patterns have deteriorated to such a degree that they can no longer live in the community. They need constant care and supervision, are a great burden to their family at home and a management problem in the hospital. It is for that reason that we have been greatly interested in reports concerning the beneficial action of oral medication by Metrazol (pentamethylenetetrazol) in senile subjects and those with cerebral arteriosclerosis.

The first report, by Chesrow *et al.* (1), on the effect of oral Metrazol in arteriosclerosis associated with senility came from the wards of a general hospital and dealt with 32 nonpsychotic but confused, bedridden, aged patients. They were given an average of 0.1 to 0.2 Gm. of Metrazol four times daily for ninety days. Marked improvement was obtained in 12 cases and fair to "some" improvement in 14 cases. Six patients did not react. Swenson and Grimes (2) treated 25 senile patients in a state mental hospital with 0.3 Gm. of Metrazol daily for thirty days, while a control group received bicarbonate tablets. Rating was carried out by physicians. No significant changes were noted. Smigel *et al.* (3) treated 20 aged patients in a chronic disease hospital with 0.8 to 1.2 Gm. daily. The subjects had a variety of illnesses, such as cancer, cerebrovascular accidents, and bone fractures. Following Metrazol therapy their appetites improved and fatigue was lessened, as was apathy and disorientation. No mention was made of a rating method or a control group. Jensen and Leiser (4) used a daily dosage of 0.3 to 1.2 Gm. in 30 psychotic, cerebral arteriosclerotic patients. Ratings by ward personnel showed moderate to considerable improvement. Results of psychologic tests (Bender-Gestalt and Wechsler memory scale) showed no significant changes. Improvement took place within the first fifty days or not at all. Fong (5) gave 36 patients with cerebral arteriosclerosis 0.4 to 1.2 Gm. of Metrazol daily for 180 days. Ratings were by physicians and charge nurses. No control group

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was used. Sixteen patients showed improvement manifested by a decrease of anxiety, fatigue and irritability.

The senile and cerebral arteriosclerotic patient confined to a mental institution generally has two groups of symptoms: 1) he is confused and disoriented and has severe memory defects, and 2) he has committed or threatened to commit acts which are not acceptable to the community. We, therefore, in our investigation took particular note of 1) changes in intellectual and psychologic functions, and 2) behavioristic changes, occurring under the influence of Metrazol medication. Standard psychologic testing procedures were used for the following functions: interpersonal relationships, memory, associative ability, body image, everyday information, self-concept, contact with reality and ability to abstract. An attempt was also made to determine mood and fatigue.

The behavior of the patients was observed on the ward. Two charge attendants volunteered to help in the investigation and checked each patient every two weeks against a behavior rating scale. This scale contained thirty-four items referring to the patient's behavior during morning and evening toilet, at bed time, his eating habits, personal cleanliness, attention to people and surroundings, and general well-being.

METHOD

In view of the intensive and extended observation program scheduled, we limited our investigation to 10 patients with 5 controls. In 6 patients the diagnosis was senile psychosis, and in 4, psychosis with cerebral arteriosclerosis. Ages ranged from 61 to 84 years. By occupation, the group included laborers, plumbers, jewelers, ministers, and carpenters. They had been patients in this hospital for periods ranging from less than one year, to more than ten years. The most constant symptoms in these patients were confusion and disorientation. One patient had set fires; others had wandered off or had delusions of grandeur or of a sexual nature; some had threatened their families; some were hallucinated; 2 patients had a history of chronic alcoholism; and in 1 case an extradural hematoma had been removed by operation two years before admission. All patients were in fair physical condition and not bedridden. The patients were given 0.1 Gm. of Metrazol orally from three to four times daily for a period of six to eleven weeks. Then followed two to three weeks of Metrazol medication with 0.6 to 0.8 Gm. daily. The maximal dosage of 0.9 to 1.2 Gm. was then given for a period of three to five weeks. The total time of therapy varied from eleven to eighteen weeks, and no other medication was given. The physical condition of the patient was checked before Metrazol was initiated and thereafter at intervals of about two weeks.

An appraisal of the progress of the patient was made by the charge attendant on the ward every two weeks, according to the behavior rating scale mentioned previously.

Each patient in the study was subjected to a series of tests consisting of the Wechsler memory scale, the figure-drawing, the Rorschach, and the Bender-Gestalt tests. Three series were given to each patient, one before medication, one after six to eleven weeks of Metrazol therapy, and one after medication was

terminated. However, one patient could not be tested. Testing usually took place at one sitting unless the subject became fatigued or disturbed.

Controls: To eliminate bias on the part of the rating attendant, a control group was checked in exactly the same manner as the experimental group. Five patients were selected from the same ward, who were of approximately the same age and mental condition. They were given placebos (handed to the attendants under the name of "Metrazol B" tablets) which had the same appearance as the Metrazol tablets. Both attendants were not aware that a control group existed but thought that Metrazol was being tested in two different forms. No attempt was made to test the control group psychologically.

RESULTS

Metrazol was well tolerated by all patients up to the dose of 0.9 Gm. daily. When the dosage was increased to 1.2 Gm. daily, 2 patients complained of weakness. One of them became cyanotic and had palpitation; the other became unsteady on his feet and acted "as if he was under sedation." In these 2 patients, as well as in a third patient who became increasingly confused and aggressive and who started soiling, medication was discontinued. Thereupon the symptoms subsided.

Behavior rating scales. Altogether the results were rather poor. No patient improved to such an extent that he could be discharged. One patient improved sufficiently to be transferred to an open ward. All changes were very slight. Occasionally patients became more alert but in some cases the initial improvement was followed by regression. Some patients became depressed during the later stages of treatment, others became more confused and deluded. One patient showed rather aggressive behavior. There was no significant difference in effect between patients who suffered from senile disease and those whose psychosis was associated with cerebral arteriosclerosis; neither did the length of hospitalization seem to be of importance.

Controls. Three of the 5 control patients did not show any change. One improved slightly during a mild intercurrent febrile disease. One patient was rated as definitely improved. He was more alert, slept less, spoke more plainly and gave brighter answers.

Psychologic testing. The tests used did not appear to be very sensitive for this type of patient, namely, severely senile, aged, disturbed psychotics. It was practically impossible to determine fatigue and mood from the meager test results. Seven of 9 patients tested were improved in certain spheres, namely, memory, self-awareness, interpersonal relationship and contact with reality. However, this improvement was not striking, often was very slight and was evident only at the time of the first re-check. No further improvement was found between the first and the second re-check. Sometimes there was a loss of the previous gain. As in the case of clinical observation, positive results were scattered among the two diagnostic groups. No relationship could be established between improvement and personality structure. Clinical improvement, as manifested by the behavior rating scale, was not always coincident with improvement found through psychologic testing, and vice versa.

DISCUSSION

Why have our results been less favorable than the results of most other observers? One reason might be the fact that we dealt with severely deteriorated patients, in whom the brain was (presumably) damaged to such an extent that functional improvement could no longer be obtained. Another reason might be that there was careful checking of our patients on a daily basis, by observers who spent eight hours daily with their patients; the judgment of these rating attendants necessarily differs from that of physicians, or even groups of physicians, who see their patients only during short interviews and not during everyday life. Most important, however, was the fact that the changes observed in the control group made us aware that oscillations in the behavior and mentation of senile and cerebral arteriosclerotic patients do occur spontaneously. Thus, it was felt that some of the changes observed in our experimental group might have been spontaneous and not necessarily due to Metrazol medication.

The basic idea of this treatment, namely, to improve brain function by combating anoxia through respiratory and circulatory stimulation seems sound. Metrazol has shown some results but must be considered as only the beginning of our therapeutic endeavor. Other stimulants or combinations might produce better results.[1] It has been known to us for a long time that Coramine (pyridine-β-carboxylic acid diethylamide) is effective in combating vertigo in old arteriosclerotic patients. Other respiratory and cardiac stimulants should be investigated.

SUMMARY AND CONCLUSIONS

1. Oral Metrazol medication exerted some action on the behavior and mentation of 10 deteriorated senile and cerebral arteriosclerotic patients. Improvement, if noted, was very slight. Results of psychologic tests showed that improvement, if any, was noted only during the first half of the experimental period.

2. Chances for improvement under Metrazol therapy seem to be related to the severity of brain damage rather than to the diagnostic label.

3. The usual psychologic test methods are inadequate for the detection of slight changes in senile and arteriosclerotic patients. New and appropriate methods should be devised.

4. The action of other circulatory and respiratory stimulants should be investigated.

5. Although this series is too small to warrant sweeping conclusions, and the controls were not tested psychologically, nevertheless we consider that the results in these carefully studied cases indicate what may be expected from Metrazol therapy in this type of patient.

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OSTEOARTHRITIS IN THE AGED

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Osteoarthritis is one of the most common causes of disability in older individuals. Such disability is manifested by stiffness and by intermittent pain, chiefly in the weight-bearing joints. Everyone over the age of 50 will show evidence of osteoarthritis upon x-ray examination. Actual disability, however, is observed less frequently—about one in ten at the age of 50. Disability increases to one in four at the age of 70. The degree of disability varies from mild stiffness and soreness after rest, to inability to walk when the hip or knee joints are severely damaged.

Comfort is the chief end of treatment in the aged, *i.e.*, those over 65 years of age (1). However, most patients are not satisfied with comfort alone. Fuller activity as well as relief of pain are essential to continued mental and physical well being. This requires that some form of useful activity or employment be found, as disability lessens (2). With the large number of individuals retired from their usual employment at the age of 65 (3), and the widening gap between the ages of retirement and death, the problem of providing some worth-while type of activity is becoming more serious each year (4). Most of these patients will be women, since statistics show that there are more women surviving than men in this older group (5).

ETIOLOGIC CONSIDERATIONS

We know many of the pathologic features of osteoarthritis but we are uncertain of its causes (6). It is believed to result in part from degenerative changes in the articular cartilage and other articular structures. These changes advance more rapidly when the joint is subjected to abnormal use. Evidence of this degeneration is seen to the greatest extent in the spine and in the lower extremities. The pathologic changes which accompany the aging process are important factors in the development of osteoarthritis. Dysfunction of the endocrine glands can be an important factor in cases of severe osteoporosis (7), but otherwise is apparently of little importance in the aged. Infection, particularly hidden infection, is considered by many as a factor in the development of osteoarthritis. Usually there is an increase of arthritic symptoms when an acute infection is present and a lessening of symptoms as the infection subsides.

SIGNS AND SYMPTOMS

Most of the symptoms observed with osteoarthritis may be explained on a mechanical basis—the disalignment of the articular surfaces and the osseous over-

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growth about the margins of the joints (8). Soreness and stiffness in the muscles and ligaments about the joints are the most common complaints. These symptoms can usually be considered as sprains resulting from overstretching or unusual pulls of the ligaments spanning the bony overgrowth at the articular margins. It has been suggested that changes in the muscles themselves, resulting from the accumulation of metabolic poisons, are the cause of soreness; this has not yet been confirmed. The same can be said for fibrositis, which is a frequent diagnosis in osteoarthritis.

As articular damage increases, synovial thickening is seen with increasing frequency and is common in the aged. This often leads to impingement of synovial fringes between the articular surfaces. Associated with this there may be fluid in the joint temporarily. With increasing degeneration, displacement of such structures as the menisci may occur. This leads to locking of the joint and to other disturbances in function. Loose bodies as a cause of impingement are not common in the aged.

One of the most troublesome symptoms, observed often in the aged, is the irritation of the nerve roots as they emerge from the spinal cord. Bony overgrowth develops about the vertebral margins and intervertebral joints, and encroaches upon the neural foramina. Irritation of the nerve leads to referral of symptoms to the cutaneous distribution of the involved nerve. Interpretation of the pain is sometimes difficult and a visceral pathologic condition may be suspected (9). Irritation of the nerve roots is seen most often in the cervical region of the spine. There is often occipital headache and pain and numbness in the shoulder and arm.

TREATMENT

Owing to our imperfect knowledge of the causes and of the changes in osteoarthritis, treatment must be symptomatic for the most part, and much of it must be mechanical in nature. The symptoms are at times confusing, being associated with the physiologic and psychologic disturbances so frequent at this age. The first problem for the physician is to assess the amount of damage in the joints and the extent of the disability. From this he can plan a program to lessen the disability and to prevent further damage. Every physiologic disturbance should be improved as far as possible. In almost every instance pain and discomfort can be relieved. Much can be done to make life more comfortable and useful. Optimism and patience are required in order to avoid passive acquiescence of disability on the one hand, or useless overtreatment on the other.

The treatment of osteoarthritis includes medical, physiotherapeutic, orthopedic, surgical and psychiatric measures. In addition, all unfavorable social and economic factors should be improved as far as possible. The chronically ill individual must be studied in his total environment. Osteoarthritis is cured by no single drug or therapeutic procedure. Temporary improvement may follow the administration of a single measure but spontaneous improvement occurs even more frequently.

Medical. In the medical treatment we include analgesics, tonics, specific medi-

cation, endocrine products and dietary regulation. Analgesics are needed when symptoms are acute. Acetylsalicylic acid or sodium salicylate is usually all that is required. If narcotics are needed to relieve pain, the presence of a more serious disease should be suspected. Tonics are usually welcomed by the elderly patient. Administration of dilute hydrochloric acid is helpful in the presence of hypochlorhydria. Hematinics, vitamin B and potassium iodide have been advocated on empirical grounds. Vaccines and chrysotherapy have no known therapeutic value. Cortisone and hydrocortisone often lead to a temporary subsidence in symptoms but produce no known alteration in the articular pathologic picture. The diet of the old patient with osteoarthritis should be high in protein and low in fat and in carbohydrate. Multiple vitamins are of value since vitamin deficiencies are common in the aged. Hormones are not often required in the aged, with the exception of estrogens and testosterone in the treatment of osteoporosis.

Physiotherapy is very helpful in these older patients (10). Rest, heat, and exercises are the chief measures used. Rest in almost all instances will bring about a temporary subsidence of symptoms. The duration of rest for the inflamed joint depends upon the severity of the symptoms. In mild involvement the use of an elastic cotton bandage may suffice. Rest in bed and the use of a plaster cast or other splint may be required in the presence of severe involvement of weight-bearing joints. Heat in any form is helpful. The patient should wear warm clothing and the house should be kept about five degrees warmer than is usual. These patients often are much more comfortable in a warm, dry climate. Heat is applied to the affected joints for periods of one-half hour, two or three times a day. All simple forms of heat are about equally effective. No more lasting effect can be expected from the more elaborately administered forms. The effect of the heat can sometimes be prolonged by the use of rubefacients, such as simple liniments.

Massage of the muscles about the joints gives comfort but is of little lasting value in osteoarthritis. No massage should be given over inflamed joints. A moderate amount of activity is much better than sitting in a chair all day. Exercises are prescribed to improve posture and articular alignment, as the better the general posture the less strain there is on the joints; these are usually performed twice daily. To improve motion in the involved joints and to strengthen the adjacent muscles, exercises are given which begin with simple muscular contractions and progress slowly to exercise against resistance. Strenuous physiotherapy is rarely prescribed in the aged. A physiotherapeutic measure sometimes of value is x-ray therapy. This is given in a dosage of 50 to 100 roentgens each treatment over the involved joint, and is usually continued until 1,000 roentgens have been given. It frequently leads to the relief of pain for prolonged periods. Its action is unknown but no harmful effects have been observed from its use.

Orthopedic therapy. Much of the disability in osteoarthritis arises from mechanical causes and its relief depends upon orthopedic, mechanical measures. Every means possible should be used to prevent or to relieve sprain at the joints and to secure better alignment and balance of the whole body. For this purpose braces and other supports are sometimes required at the wrist, elbow, spine and weight-bearing joints. Good, well-fitting shoes and supports for the arches of the

feet help when there is strain on the feet and knees. When osteoarthritis is present in the spine, with pain and stiffness, a spinal support or a corset may relieve symptoms and prevent a recurrence. In very severe symptoms a plaster or plastic jacket supporting the entire spine may be necessary. When there is spinal involvement the patient should sleep on a firm bed and the back should be firmly supported by the chair in which the patient sits. Sometimes supports must be worn continuously at the hip or knee when these joints have been damaged severely. Crutches are very helpful temporarily to relieve symptoms in the weight-bearing joints, particularly the hip joints. Continuous traction is of value in the treatment of muscular spasm and pain in the cervical spine and in the hips; this must sometimes be continued for a week or longer. Traction is helpful in preventing irritation of the nerves emerging from the cervical spine for a few weeks after spasm and pain have been relieved.

Surgery, although a helpful measure in the correction of deformities in severe osteoarthritis, is not required very often in older persons (11). Surgery is employed for two purposes: 1) to relieve pain, and 2) to improve function. Pain that sometimes requires surgery for its relief is found in severe osteoarthritis in the cervical or lumbar spine. Bony overgrowth about the foramina or degeneration of the intervertebral discs may lead to such pressure upon spinal nerves that surgical decompression is necessary. In the upper extremity, surgery is employed almost exclusively for the removal of bony spurs or inflamed bursae. One of the most severe disabilities in osteoarthritis occurs at the hip joints. When severe flexion and adduction are present, surgery may be required to make walking possible. Sometimes deformity can be lessened by manipulation of the hip under anesthesia. The effect can often be prolonged by an intraarticular injection of hydrocortisone. An obturator neurectomy, with section of the nerves to the external rotators of the hip, will often relieve pain but rarely improves function. When there is severe fixed deformity of the hip, replacement of the femoral head by a metallic prosthesis often is followed by relief of pain and by reasonable function. In the knee, surgery is used to relieve impingement from a loose body or from a degenerated semilunar cartilage. In the foot, the problems of osteoarthritis are the same as in static disabilities, and the same procedures are employed. Extensive reconstructions of the joints are almost never performed in the aged. If the electrolyte balance and the blood volume are maintained, elderly patients withstand surgical procedures surprisingly well. The anesthetic is usually given by the spinal route. Long immobilization of the body in one position should be avoided. When possible, the patient should be out of bed the day following operation. Breathing exercises are given for the first postoperative week, to prevent venous and pulmonary complications.

Psychiatric treatment is important but it is employed most effectively when the patient does not recognize it as psychiatry. It is least necessary for the cheerful, well-adjusted person living in his own home. It is of little if any value in patients in their dotage or in a state of advanced senile dementia. Such treatment consists as much of cheerfulness coupled with patience and understanding, as it does of the employment of special psychiatric techniques. Many of the nervous and mental changes cannot be reversed but their progression can be slowed; not

all of them are the result of degenerative and circulatory changes. Although some alteration in the personality almost always accompanies the aging process, the tactful physician can usually get satisfactory cooperation. Much of the psychotic behavior is often precipitated by anxiety and is increased by poverty, frustration and resentment. This is seen particularly in osteoarthritis when the disability is such as to prevent the aged individual from caring for himself or from earning enough money to provide the necessities of life. As observed in arthritis clinics, the triad causing mental ill health consists of unemployment, inadequate resources and a feeling of not being wanted. Usually acute psychotic episodes can be relieved much more effectively than those of long duration. It is important for the physician to recognize the organic character of some of the complaints related to psychiatry and to separate these from the functional ones. Improving the patient's environment and then helping the patient to adjust to it, are important parts in the treatment of the elderly arthritic (12).

SUMMARY

The treatment of the elderly individual with osteoarthritis differs from that of the younger individual chiefly in the emphasis on aims, in the employment of less strenuous procedures and in the attempt to bring about a better adjustment to the illness and to the environment. Although comfort is the chief aim, useful activity or part-time employment is usually essential. There are no specific medicines; nevertheless tonics, vitamins and proper supervision of the patient's diet are helpful. As much activity as the damaged joints will tolerate, together with heat and exercises, usually produce improvement. When there is severe damage, simple, light supports will often make it possible to use the joints painlessly. Surgery is rarely employed for osteoarthritis in the aged but is helpful in the amelioration of severe fixed deformities. Psychiatric treatment is often of value in adjusting to permanent disability and to an unfavorable environment.

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INCIDENCE OF CARCINOMA AND SECONDARY OPERATIONS FOLLOWING SUBTOTAL PROSTATECTOMY IN 617 PATIENTS

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The life expectancy of elderly males currently being subjected to major prostatic operations to relieve obstruction is greater than ever before. According to actuarial tables (1), the 65-year-old man has a life expectancy of thirteen years. This means that long-term results of operations for prostatism must be scrutinized.

An over-all operative mortality rate of 3 per cent was reported by Shivers and Groom (2) in 14,865 operations for benign prostatic hypertrophy. Others have reported lower rates (3, 4, 5). In Shivers and Groom's series, the incidence of postoperative morbidity (persistent obstruction, infection, or residual urine) was 8.4 per cent. Johnson and Gunderson (5) had a morbidity of 19 per cent. An incidence of 12.1 per cent for secondary operations performed at an average of 6.7 years after the first transurethral prostatectomy, was reported by Taylor and Place (3).

Carcinoma may develop in the posterior portion of the prostate gland not removed by simple prostatectomy or resection. In Bakalim's series (6) there was an incidence of 8.7 per cent for carcinoma developing after suprapubic prostatectomy, and in Young's series (7) the incidence was 11.5 per cent after transurethral resection.

Edwards, Steinthorsson and Nicholson (8) reported an incidence of 3.5 per cent for clinical carcinoma of the prostate in an autopsy series; an additional 18.7 per cent of prostates showed latent cancer. The latent prostatic carcinoma was often multiple, but in 77.7 per cent the foci of malignancy were in the posterior lobe. The average age of the patient in the cases of latent carcinoma was 68.1 years as opposed to 72 years for the clinical type. Latent carcinoma occurred 2.7 times more frequently in hypertrophied prostates than in normal prostates. These results are in agreement with the earlier similar studies of Moore (9) and Andrews (10).

Clinical carcinoma of the prostate gland amenable to radical cure constituted only about 11 per cent of Jewett's cases (11). Inoperable carcinoma of the prostate gland responded to certain hormonal control measures promoting longevity and alleviating pain. Huggins and his associates (12, 13, 14) have indicated that orchiectomy, estrogen administration and adrenalectomy have their place in managing inoperable prostatic carcinoma. Nesbit *et al.* (15, 16) showed that the three-year survival rate for patients treated by orchiectomy and administration of estrogen was 66 per cent, when there were no metastases at the time of initiation of treatment; it was 25 per cent when there were metastases. In an untreated series, the three-year survival rate was 22 per cent. Barnes (17), in a

selected series of early carcinomas of the prostate, found endocrine-treated patients had a five-year survival rate of 53 per cent and a ten-year survival rate of 22 per cent, but 36 per cent had persistent carcinoma. West and associates (18) reported that following adrenalectomy in 17 cases of advanced carcinoma of the prostate the average survival time was five and a half months. Jewett (11) found that radical prostatectomy in suitable cases gave a five-year survival rate of 51 per cent and a ten-year survival of 28 per cent without recurrence. Culp (19) stated that impotence almost inevitably followed radical excision of the prostate gland. Smith (20) said that 80 per cent of patients had good urinary control after radical prostatectomy. Scott (21) added to the number of operable cases of carcinoma of the prostate gland an additional number of locally invasive carcinomas in which a favorable response to endocrine control measures permitted subsequent radical excision. His three-year survival rate was 85.7 per cent, compared to 66 per cent reported by Nesbit and Baum (16) in their series treated by orchiectomy and stilbestrol. Smith (20) and Hand (4) applied the indications for total prostatectomy rather generously, erring on the side of excision when doubt existed as to the nature of a suspicious nodule.

From this background in the literature it may be reasoned that present-day subtotal prostatectomy yields as high as 20 per cent undesirable immediate results, leads to re-operation for obstruction in as many as 12 per cent of the cases, leaves tissue behind which develops into clinical carcinoma in from 8.7 to 11.5 per cent, and contains an occult carcinoma in an additional 14.5 per cent.

For comparison, the following case analysis was made.

CLINICAL STUDY

Six hundred and seventeen patients undergoing prostatectomy at King County Hospital from January 1, 1947 through September 30, 1952 were studied. Of these, 504 patients, or 88.2 per cent, had benign hypertrophy. Their average age was 74.3 years at the time of the first operation at King County Hospital. There were 691 prostatic operations, including those performed elsewhere. Of these, 120 (22 per cent) were secondary. Primary prostatectomy by open operation (194 cases) required re-operation 17 times (3.1 per cent). Primary prostatectomy by transurethral resection required re-operation in 113 cases (20.9 per cent). Grouping the secondary operations by time intervals after the primary operations showed that 37.6 per cent of patients had to be re-operated upon within three months. Only 13 patients had more than two prostatic operations for benign hypertrophy. One patient had six operations in fourteen years for the removal of 116 grams of prostatic tissue.

In 10 patients (1.6 per cent of the series) carcinoma of the prostate was known to have developed following prostatectomy for benign hypertrophy. The interval ranged from three months to nine years, with an average of four years.

The group of 73 patients (average age 74.7 years) with malignant disease of the prostate at the time of the first operation had 113 prostatic operations, of which 84 per cent were transurethral. Secondary resections were performed in 28 cases (38 per cent).

Only 20 per cent of the patients were known to be dead from all causes at the

end of the observation period. Because of the free nature of the medical service provided, follow-up of the patients left something to be desired. However, patients were prone to enter the hospital for terminal care and the mortality statistics are probably reliable. Only 47 patients died from all causes during the first postoperative month. This was a mortality rate of 5.8 per cent for 804 operations.

DISCUSSION

In the foregoing series of 804 operative cases (Table 1) we were surprised to discover that in only 1.6 per cent of patients undergoing subtotal prostatectomy did clinical carcinoma subsequently develop. This was much lower than the incidence reported by Bakalim (6) and Young (7). The average age of patients was 74.3 years—about nine years more than the average age (65.4 years) of patients undergoing 1,500 retropubic prostatectomies in the series reported by Millin (22). It may be that in patients of this higher age-group the tendency to clinical malignancy is already manifest and the risk of clinical carcinoma decreases. We cannot conclude from the data presented that subsequent malignant degeneration of the posterior prostatic lamella would constitute statistically valid indication for total prophylactic prostatectomy at the time of the first prostatic operation.

Transurethral resection was often deliberately planned in stages, so as to avoid the greater risk of a more prolonged complete procedure. In the series of patients presented, among the 24 per cent requiring repeated operation, 86.5 per cent had had initial transurethral resection. Their cases would probably have been better managed by open subtotal excision of the prostate or by total prostatectomy.

In patients 10 years younger the greater risk of clinical carcinoma, with its low rate of cure, might suggest total excision of the prostate at the time of the first operation. A great deal might be accomplished in decreasing morbidity, re-operation and the subsequent development of carcinoma, at the small cost of a greater incidence of impotence. It is immaterial whether the total prostatectomy be performed by Young's classic method (23), by one of its modifications (Vest (24) and Belt (25)), or by the retropubic approach popularized by Millin (22) and

TABLE 1

	Benign hypertrophy		Carcinoma	
Number of cases	544 (88.2%)		73 (11.2%)	
Age at first operation	73.4 years		73.4 years	
Age at first operation (King County Hospital)	74.3 years		74.7 years	
Number of operations	691		113	
Type of first operation	Open	Transurethral	Open	Transurethral
	231 (33%)	460 (67%)	18 (16%)	95 (84%)
Subsequent operations	17 (3.1%)	113 (20.9%)		28 (38.4%)
Carcinoma developed later	10 (1.6%)			

admirably described by Chute (26). All techniques are effective in experienced hands and well tolerated by aged patients.

SUMMARY

A review is presented of the literature pertaining to the incidence of morbidity, re-operation, postoperative late malignant degeneration of the prostatic capsule and latent prostatic carcinoma. According to the literature, subtotal prostatectomy may give poor symptomatic results in 20 per cent of patients and lead to re-operation in up to 12 per cent. Clinical carcinoma of the remaining prostatic tissue may develop in 11.5 per cent, and latent carcinoma in 14 per cent of patients. Thus, subtotal excision of the prostate may yield undesired results in numerous cases in which total prostatectomy might have been employed. On the other hand, although total prostatectomy renders many patients impotent, only about 20 per cent of patients show other undesirable results. Moreover, there is no possibility of postoperative prostatic malignancy.

An analysis is presented of 804 prostatectomies performed on 617 patients with an average age of 74.3 years. In 88.2 per cent the diagnosis was benign prostatism, and the inital procedure was subtotal prostatectomy. Of these cases, 18.6 per cent required one or more re-operations for relief of obstruction. In an additional 1.6 per cent clinical carcinoma developed in the unremoved portion of the prostate.

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CARDIOVASCULAR SURGERY IN GERIATRICS*

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The expanding field of cardiovascular surgery has in the last decade encompassed some of the vascular problems in geriatrics. There are many facets to this expansion of the scope of vascular surgery. However, of paramount importance has been the equal and simultaneous progress in anesthesia, the increased knowledge and awareness of blood and fluid requirements and an understanding of body chemistry. The great advance in the control of infection by antibiotics and chemotherapeutic agents has added its part to this expansion.

The main pathologic condition encountered in geriatrics is arteriosclerosis. Although all authorities agree it is a generalized disease, it is grossly characterized by "skip areas," *i.e.*, the lesions are confined to segments. There is thus an element of localization which permits therapy to be directed at the involved region.

CORONARY ISCHEMIA

This pathologic change in the myocardium was one of the first degenerative cardiac lesions to come under the surveillance of surgeons. Historically, there have been numerous attacks upon this lesion, ranging from excision of the acute myocardial infarcts as suggested by Murray (1) to the use of an arteriovenous fistula as proposed by Beck (2). Since ischemia of the myocardium is heralded by incapacitating pain and is a warning of future myocardial damage or acute coronary occlusion, O'Shaughnessy (3) used surrounding organs in attempting to increase collateral circulation to the myocardium and finally decided that omentopexy was the best procedure. His results were not dramatic but he was persistent in his attempts to improve the circulation to the myocardium through a non-damaged vascular system. Carter (4), in this country, also pursued this line of endeavor and followed Lezius (5) in reporting good results with clinical studies. Fauteux (6) approached the problem from the neurogenic standpoint, performing periaortic neurectomy and ligating the coronary sinus. This procedure had given him excellent results in animals, but the effect in human subjects was not dramatic. Probably the most outstanding American investigator in this field has been Beck (2, 7, 8, 9). His earlier attempts were aimed at producing an adhesive pericarditis in an effort to increase the collateral circulation, or using the thoracic musculature in an effort to support an increased collateral circulation to a damaged myocardium. However, in the last six years his efforts have been totally directed toward the production of a controlled arteriovenous fistula between the aorta and the coronary sinus, in an effort to deliver to the myocardium oxygenated blood through a vascular system which

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has not been impaired by arteriosclerosis. His results have been dramatic, and although the operative mortality is above that which we would prefer to deal with, it is not as great as that of the disease itself. We favor the use of this attack upon myocardial ischemia and have found that the results are most satisfactory. Bailey (10) of Philadelphia, has written of his experience with this procedure and considers it the method of choice in people who have angina decubitus or severe myocardial ischemia, as shown by physiologic testing with exercise.

The statement that all patients suffering from coronary ischemia are surgical cases is obviously a fallacy. In fact, to undergo such an operation as the two-stage procedure of Beck or the transpleural operations of Carter, a patient should be relatively young if a satisfactory outcome is to be anticipated. The procedure of inserting 2 drams of sterile U.S.P. "talc" through the fifth costal cartilage bed is well tolerated by severely debilitated patients, and gives dramatic results in long-term clinical investigation, as reported by Thompson (11, 12).

Shoulder-arm-hand syndrome: This is one of the less severe complications of coronary ischemia but patients with this syndrome are as incapacitated as those with angina decubitus.

The etiologic factor is myocardial ischemia, but the nervous pathway of the referred pain is difficult to chart. Block of the cervical sympathetic trunk often brings prompt relief. The surgeon can put such relief on a permanent basis by dorsal sympathectomy. This procedure may be carried out extrapleurally from a posterior approach, entails little risk, and is almost certain to relieve symptoms.

ANEURYSM OF THE HEART

An aneurysm of the left ventricle is usually secondary to myocardial infarction. This lesion often goes unrecognized or is mistakenly diagnosed as a metastatic tumor of the lung. The softening and thinning of the infarcted myocardium leading to an aneurysmal dilatation is a threatening complication of myocardial infarction. There are two methods of surgical attack on this lesion, both of which are without great risk to the patient and considerably lessen the mental apprehension on the part of both patient and attending physician. If the aneurysm is not too large, an actual excision with resuture of the myocardium is possible. If the aneurysm is too large to be removed, a pericardial patch may be sutured to the myocardium itself, in an effort to strengthen the thin myocardial area. It is obvious that the former attack is preferable, as substantiated by the experimental work of Carter (13) and Murray (1) on the excision of full-thickness myocardial strips.

The patient with acute coronary occlusion often presents himself with severe hypotension. This complication is usually considered a grave prognostic sign and presents many problems to the attending physician. The internist is often hesitant to transfuse a patient who is in a state of extreme shock with hypotension, due to the fear of increasing the load on an already damaged myocardium, and yet he wishes to maintain an adequate blood pressure for oxygenation of the vital centers and coronary system. It is within the realm of possibility

that the surgeon can be of some benefit in the near future in such a crisis. The use of a pump oxygenator which would divert some of the blood from the superior vena cava and redistribute it to the arterial system without going to the lungs and heart would be, in a sense, a splinting of an already damaged cardiac muscle. Such use of an extracorporeal pump-oxygenator system would be a great stride in the abatement of acute coronary occlusive shock with its high mortality. There are at present only a few institutions in the United States which are equipped with such a mechanism, but the expansion of such service can be foreseen.

The shock associated with myocardial infarction was experimentally reproduced in animals by Murray (1). The mechanism of production was a paradoxical systole with resultant incomplete emptying of the left ventricle. The excision or strengthening of the infarcted area was followed by restoration of the blood pressure to normal levels. Therefore it seems possible that the surgeon could be of aid by a direct surgical attack upon the heart in patients with acute myocardial infarctions complicated by shock.

ARTERIAL ANEURYSM

Since the time of Antyllus, aneurysms of the great and peripheral arteries have been a surgical problem. Arteriosclerosis is a generalized disease but, because of its segmental distribution, at times it manifests itself as an aneurysm. Pathologically, most ascending aortic aneurysms are luetic and most descending and abdominal aneurysms are arteriosclerotic. Rupture of any of these aneurysms is 100 per cent fatal. The time of rupture cannot be predicted; it may take years, or may be only a matter of minutes. Therefore the best therapy is prophylaxis; otherwise, the excision and replacement or reinforcement of the affected segment is the only adequate treatment at the present.

There are three methods of surgical attack upon such lesions. First, and without doubt the most sound, is actual excision and replacement. Second,—less adequate, but at times the only possible method—is the wrapping or the reinforcement of the aneurysm to prevent rupture. Third, is the wiring or packing off of the aneurysmal cavity in an effort to cause thrombosis within the sac and thus lessen the possibility of rupture. Experience is being accumulated by us and by Bahnson (14) and others (15) on the excision of these aneurysms and re-establishment of vascular continuity, either by plastic repair or by the use of preserved homografts. It has been well established that large segments of the thoracic and abdominal aorta may be removed and replaced by adequate new tissue which will carry the circulation without threat of rupture. We have also wrapped a number of abdominal and thoracic aneurysms, with good results in the immediate postoperative course. However, 2 patients returned, 1 after two years and 1 after four years, with extension. The aneurysms had to be rewrapped and wired in an effort to prevent further rupture. Blakemore (16) in New York has proposed the wiring and coagulation of saccular aneurysms, and proximal ligation and wiring of fusiform aneurysms, in an effort to prevent rupture. The usual method of wiring is tedious and at times too severe a surgical procedure

for an acutely ill patient. We have devised a method (17) by which, under local anesthesia, four to five hundred feet of wire may be run into an aneurysm within a matter of minutes. The method of pack wiring proposed by Linton (18) is thus accomplished without too much trauma to either the patient or the surgeon. There is little doubt that the correct line of surgical attack upon aneurysms is their excision and replacement. This has been accomplished both in the thoracic (19) and abdominal regions in elderly patients who have, with modern anesthesia, tolerated long procedures extremely well. As shown by experimental work (20), homogenous arterial grafts preserved in a nutrient medium, or lyophilized grafts, used as prostheses have proved to be feasible, and the clinical results have been satisfactory.

OBSTRUCTION AT THE AORTIC BIFURCATION

Obstruction at the bifurcation of the aorta, commonly referred to as the Leriche syndrome, has been of particular interest to the surgeon. In the middle and older age group, arteriosclerosis at the bifurcation and in one or both iliacs has been a common finding in people who have peripheral vascular ischemia. Two surgical procedures have been proposed: 1) thromboendoarterectomy, as originally described by dos Santos (21), and used by Wiley (22) in this country, and 2) excision and replacement of the bifurcation and involved aorta and iliacs. Our results with thromboendoarterectomy have been most disappointing and we now prefer the second method. This approach has almost universally given excellent results and no postoperative complications have occurred. The correct diagnosis and the planning of the surgical attack is dependent upon x-ray delineation of the aorta and adjoining vessels, which may be obtained without difficulty for patient or surgeon. Patients who have obstruction of the aorta will obviously stand clamping of this channel for an indefinite period. Thus a replacement can be made without risk, and it is possible to perform a careful dissection and removal of the diseased vessel, as well as a careful suturing when putting the prosthesis into place. All of these factors lead to a low mortality and morbidity with gratifying postoperative results.

ARTERIOSCLEROSIS OF THE FEMORAL VESSELS

When the major part of the vessel is not markedly narrowed, large segments of an arteriosclerotic femoral vessel may be removed, and replaced by a vessel with an adequate lumen. In many older individuals the narrowing is confined to segments. In such instances the blood flow to the extremity may be improved by resection of the sclerosed areas and replacement by vein graft (23). Arteriosclerosis associated with diabetes is likely to be generalized and "skip areas" are unlikely. We have used arteriovenous anastomosis in the femoral region as a means of carrying blood to ischemic legs and feet, but the results have been disheartening, especially in the arteriosclerotic patient. It is a temporary measure at best, and its use is not recommended when other more direct and adequate procedures are possible. In the older age group it is quite unlikely that use of a distal vein to carry oxygenated blood to an extremity will afford much relief

from ischemia, since the anastomosis must be made to an inadequate femoral artery.

Lumbar sympathectomy, despite the subsequent lack of objective changes in an arteriosclerotic limb, does offer some relief from pain and in many instances allows the patient who would otherwise be completely incapacitated to carry on. Dilatation of arteriosclerotic vessels is not to be expected following lumbar sympathectomy and the improvement must come from dilatation in the smaller vessels. The increase of blood flow is not great following sympathectomy in the arteriosclerotic patient, but even a small increase may be sufficient to meet the demands of the elderly patient.

CONCLUSION

Advances in vascular surgery have brought many of the crippling disorders of the older patient into focus. Problems are discussed which formerly were considered to be a natural result of aging and without possibility of relief. Attempts to correct vascular defects in older individuals have had gratifying results. Many patients can continue their activities with comfort, who otherwise would lead lives of invalidism and suffering. With most of them, any possibility of relief is so desirable that the dangers and discomfort of the operative procedure are usually not too disquieting.

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SENILE CHANGES OF THE SKIN IN MAN

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It is difficult to decide what skin changes should properly be regarded as being dependent upon age itself, when the larger question of tissue aging is still something of an enigma (1). A variety of small tumors may be found on the skin of old people but they are by no means unknown in comparatively young adults; these are seborrheic warts, papilloepitheliomata (or skin tags), senile (or acquired) angiomata, senile keratoses, basal-cell carcinomata and squamous-cell carcinomata (2). Most of the dermatoses that affect young adults are also to be found in old people, in which case some special clinical problems arise (3). This discussion concerns the general changes in the skin most closely correlated with senescence, together with a few less well recognized clinical entities.

We are inclined to take the appearance of aging at its face value, but it should be realized that sunlight is responsible for most of the changes of exposed skin with advancing years. In deciding what changes are related to aging, it is necessary to consider the skin normally covered by clothing separately from the weatherbeaten areas.

MECHANICAL CHANGES DUE TO AGING IN COVERED SKIN

Gross appearance

The surface of old skin appears wrinkled and a little more shiny than that of young skin and there is a tendency towards dryness and cracking of the horny surface layer (Fig. 1). If the skin is pinched between finger and thumb, the released skin returns slowly into place and one gets the impression that it is thinner than normal and lacking in elasticity and turgor. Besides the coarse wrinkles over flexures and in relation to muscles of expression, there are innumerable very fine wrinkles consequent upon atrophy of the dermal papillae and flattening of the epithelium, and these fine wrinkles steadily increase with age (4). The loss of subcutaneous fat commonly observed in senescence leads to a redundancy of skin which is no longer sufficiently elastic to take up the slack; thus flaccid folds appear. Differences between the hydration of the skin and of the subcutis may also lead to this kind of folding of the whole skin thickness.

Measurement of mechanical properties of the skin

An apparatus was designed by Schade in 1912 (5) to measure the elasticity of living skin, and various modifications of this "elastometer" have been used since then (6). A metal knob is weighted down onto the skin; then the vertical movements of this knob are amplified by a connected side arm and recorded

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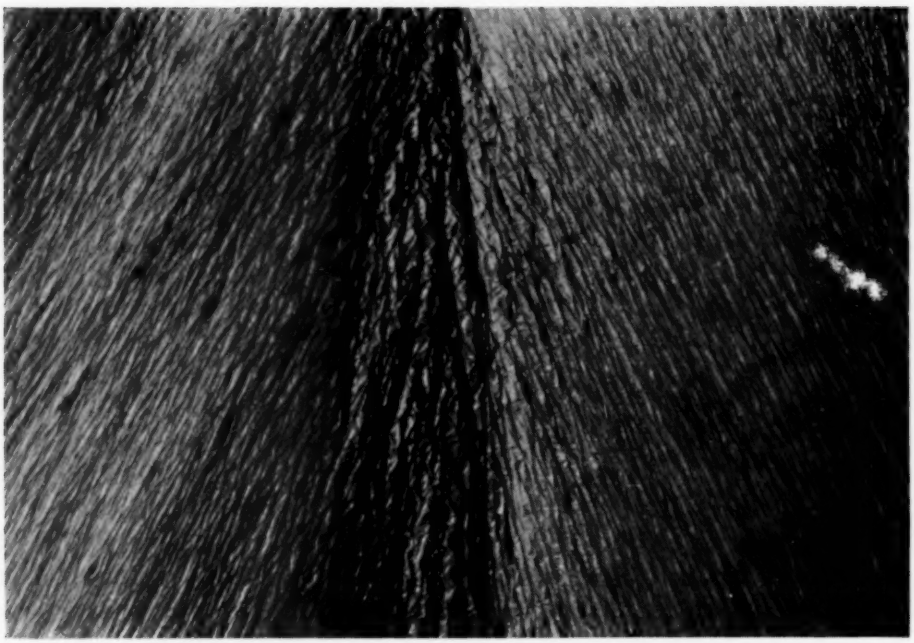

FIG. 1. Skin of the back in old age, showing fine wrinkling, folding, and dry, shiny surface.

on a revolving drum. The extent and rate of indentation and rebound of the skin are measured. These factors decrease with age, as shown by measurements on comparable skin sites.

Dick (7) used excised discs of skin which he fixed in place over a fluid-filled cylinder. The movements of the center of the skin membrane under increasing loads from the fluid beneath could be amplified and recorded and gave a measure of stretchability of the skin. He also noticed that a disc of skin would shrink on excision, and pointed out that normally the skin is in a slightly stretched state. Dick (8) had already studied the normal distribution of elastic fibers in the human skin and was able to relate the decline in elastic tension and laxity under small pressure loads with aging to a decreased distribution of yellow elastic fibers. In the abdominal skin, where the dermis is thick but the elastica is sparse, this particular age change is not apparent, whereas on the lateral aspect of the thigh where the elastic fibers are numerous and where the total thickness of the dermis is less, the loss of elasticity with age is pronounced. This measurement only refers to small distorting loads applied to the skin; with greater loads it is the collagen which resists stretching. Chieffi (4) suggests that the pilomotor muscles may play a part in normal skin tension.

Tensile strength and extensibility

These depend upon the condition of the collagen and ground substance and their state of hydration. In the infant the skin shows great extensibility and low tensile strength (9). The extensibility of the skin steadily decreases with aging and the tensile strength increases. Rollhäuser (10) visualized a tendency for

the collagen fibers to intertwine and mesh together in older skin when stretched, thus resisting extension. Loss of water from connective tissue in older persons would reduce the power of the collagen fibers to slip over each other.

ANATOMIC CHANGES DUE TO AGING IN COVERED SKIN

The dermal papillae

During aging, the most consistent change towards what is generally called atrophy is the shrinkage of the dermal papillae. The dermal vascular papillae, which in young skin indent the deeper aspect of the epidermis and interdigitate with the rete ridges, are flattened in old skin and lack the delicate elastic fibers which radiate towards the epithelium.

The epidermis

The flattening of the basal layer of the epidermis is secondary to shrinkage of the dermal papillae. Most observers also state that the epidermis is atrophic, but there is no general agreement as to whether there is a diminution of epidermal thickness with age, or whether there is any consistent change in the granular layer. Cooper (11) considered that the fine superficial wrinkles of old age were due to epidermal atrophy, but Evans *et al.* (12) thought that any apparent atrophy was a spurious change dependent upon the contours and state of hydration of the dermal papillae.

The adnexae

Although there is a tendency towards diminution of body and scalp hair with aging, after maturity some coarse hairs on the exposed parts may increase. The patterns of hair loss and of hair depigmentation are so variable and depend so much upon genetic factors that these will not be discussed. Sebaceous glands and sweat glands are anatomically preserved in older skins, though in some sites the function of both types of gland is generally assumed to be diminished with age. On the face and scalp, large and actively secreting sebaceous glands may persist into old age.

Connective tissue fibers

Microscopic assessment of changes in elastic fibers with age is difficult and has to be carefully related to the normal distribution for the part of the body under consideration (8). Uncertainty over the role of elastic fibers in the senile changes of exposed skin has led to confusion in the past. On covered parts of the body there is, besides the loss of fine elastic fibers from the papillae, a loss of elastic fibers from deeper in the corium (13), and there are qualitative changes in the elastic fibers remaining (8).

There appears to be a diminution in total bulk of collagen in old age and Strobel (14) found that the fiber bundles showed packing into parallel arrays more prominently in old skin. These changes are not easy to appreciate under the microscope and some observers have doubted that any consistent diminution of fibers could be demonstrated.

Ground substance and hydration

It is probable that the skin owes much of its elasticity to hydration of its ground substance as well as to the connective tissue fibers. Gersch and Catchpole (16) studied the ground substance of the skin in rats at various ages. In the newborn animal the ground substance is copious and easily extracted with water. As aging takes place the amorphous ground substance decreases, the connective tissue fibers increase, and the basement membranes between epithelial and endothelial structures and connective tissue stroma differentiate. Gersch and Catchpole believe that the ground substance polymerizes and loses its solubility in water; and that the depth of staining with metachromatic and vital dyes will vary with its state of polymerization. The ground substance of the skin contains nonfibrous protein and mucopolysaccharides (chondroitin sulfuric acid and hyaluronic acid) together with tissue fluid. This forms a jelly-like continuum between fibers, vessels and other structures of the skin, and a cement between the fibrillae which make up the connective tissue bundles (17). The basement membranes are probably special condensations of ground substance which have the argyrophilic reticulum fibers set in them. The mucopolysaccharides of the ground substance are thought to be of particular importance in binding water in the skin, and in the passage of electrolytes through the skin.

Gross has also commented on the amorphous material clinging to connective tissue fibers of skin when these are prepared for electron microscope examination. This interfibrillary material becomes less with age, but also becomes more difficult to remove from older dermal fibers, as it is no longer easily water-extractable as is the copious ground substance of the infant (18, 19). Changes in permeability are observed in the skin during aging (20), but the state of the ground substance is not the only factor; it is also necessary to consider the lymphatics and blood vessels.

EFFECT OF HORMONAL CHANGES DUE TO AGING ON COVERED SKIN

In the presence of aging, changes in hormone balance may significantly affect the skin. In panhypopituitarism in young subjects (progeria, for instance) the aspect of extreme old age includes senile appearance of the skin. It might be argued from this observation that the changes occurring in the skin in old age are the result of gradual failure of pituitary function. However, in senescence, the failure is mainly on the part of organs normally dependent upon the pituitary for their stimulation. In old age the pituitary-adrenal axis is still capable of active response, though the reaction is less acute than in youth. In fact, with aging, a gradual increase of gonadotropic hormone has been measured, similar to that which is found in castrates (21). In senescence, there is a deficiency in the gonad itself, manifested in the male by a very gradual decline in the function of the interstitial cells of the testis, and in the female by a more abrupt failure of estrogen production by the ovaries after the menopause. The decline in androgen production is reflected in the gradual fall of urinary 17-ketosteroids in both

sexes with aging (22). There is however no exact correlation between 17-ketosteroid excretion and degree of skin change (23).

Turning for a moment to observations with sex hormones in animals, a very striking effect is that of estrogen upon the perigenital skin of the female rhesus monkey (24). At estrus this skin swells enormously and the estrogen appears to stimulate dermal fibroblasts in these areas to the production of an excess of mucopolysaccharides, which accumulate in the interfibrillary ground substance. Prolonged administration of estrogen causes similar accumulation of mucinous hygroscopic material in skin remote from the genital area. In the cock, testosterone is largely responsible for stimulation of the connective tissue cells in the intermediate zone of the comb, which then owes its turgor to the marked accumulation of ground-substance mucopolysaccharide and water, along with an increase of vascularity (25).

It is probable that besides having characteristic effects in sex areas, the sex hormones influence the dermal connective tissue throughout the body. Under their influence, fibroblasts control the mucopolysaccharide content of ground substance; this mechanism is particularly important in holding electrolytes and water in the skin, and so influencing its turgor and elasticity. Marson (22) found a low serum sodium level in old age and suggested a relationship with the diminution of extracellular fluid volume.

Obviously there are many other factors besides the sex hormones that may influence the skin. Pituitary growth hormone has some influence on fibroblast activity (26, 27), and the balance between thyrotropic hormone and thyroid function influences the ground substance of the skin (17). The maintenance of homeostasis between numerous conflicting influences is extremely complicated (28). Sex hormones have received most attention because of the pronounced effects of unphysiologic doses.

Experimentally, local applications of hormones have a distinct effect, for instance, that of estrogen ointment on the thin inelastic skin of old women (29). As a control, the ointment base may be applied to the opposite side of the body (30). After application of estrogen for thirty to fifty days there is usually an increase in turgor and elasticity of the treated region as compared with the control, there having been no general estrogen effect on the rest of the body. Measurement of the increase in elasticity was made by Chieffi (31), using the type of elastometer already mentioned (6). Evidence derived from comparison of histologic appearances in biopsy specimens obtained from both treated and control areas is difficult to assess, as the changes are very slight. From a considerable amount of work, it seems clear that estrogen produces in the aged female skin an increase in the size of the dermal papillae, with a corresponding increase in the size of the rete processes between them. Whether there is any true or sustained increase in the thickness of the epidermis or in the condition of the deeper dermal connective tissue fibers is uncertain. It seems most likely that the main change is one of hydration of the dermis, especially the dermal papillae, though some increase of fibroblast activity is probable. The situation

in the aged skin is somewhat similar to that in bone during senile osteoporosis. Osteoporosis may be corrected by the anabolic hormones which stimulate osteoblasts to produce more stroma (32).

Estrogen ointments have no local effect when applied to the skin of young women, nor is there any effect in old men. Testosterone is said to have an effect on old skin of either sex, with a definite epithelium-stimulating action, and apparent production of papillary regeneration (30).

The local effects of the sex hormones are of research interest, but it is unlikely that they have any long-term beneficial effect on senile skin, and there is even a possibility of their producing either atrophy, or a carcinogenic effect (30).

EFFECT OF AGING ON EXPOSED SKIN

Genetic factors

Genetic factors are of greatest importance in determining the resistance of the skin to the damaging influences of environment. The horny layer serves to filter out much of the particular wave length of near ultraviolet light (Ca. 2900 Å) which is responsible for sunburn erythema; thus the thickness of the horny layer is of importance in this regard. Another screen is provided by melanin, which is formed by melanocytes in the region of the basal layer of the epidermis and which is carried up as a fine dust with the epidermal cells. Many fair skinned peoples are deficient in these two respects, whereas the darker skinned have more melanin pigment and a thicker horny layer and, in consequence, are much better equipped to live in sunny climates. Occupation and climatic environment are obviously important and one has only to consider the high incidence of "senile skin," keratoses, and carcinomata of the skin in people of Anglo-Saxon descent working on ranches in very sunny regions of Australia and southwestern United States to be convinced of this. It is noteworthy that reaction to sunburn is followed by compensatory hyperkeratosis and hyperpigmentation, both of which protect against further sunburn.

Xeroderma pigmentosum. The most unfavorable genetic influence is seen in xeroderma pigmentosum. This is a rare Mendelian recessive condition, which is manifest in early childhood. Exposure to sunlight results in an extreme reaction involving excessive inflammation followed by dryness and scaling, deep brown freckles, and areas of depigmentation and keratoses which may develop into carcinoma at an early age. Either basal-cell or squamous-cell carcinoma and even malignant melanoma may occur and the unfortunate members of these families usually die young from these malignant growths. Microscopically, besides the epithelial changes related to carcinoma formation, there are found at an early age all the features of "senile elastosis" (33) which will be described. Consideration of xeroderma pigmentosum calls into question the whole problem of the *relationship between cancer and age*. Experimentation with susceptible strains of mice brings out the point that in young skin exposed to carcinogen epithelioma develops as readily as in old skin, or indeed more readily in some strains (34). In relating development of carcinoma to

older skin, it must be remembered that age allows repeated exposure to slowly operative carcinogenic influences rather than in any way predisposing to cancer.

Senile elastosis

Although this change in the skin is dependent upon light rather than upon age, it is such a common accompaniment of old age that it should be considered in some detail.

At the back and sides of the neck the skin is tinged with yellow and is somewhat thickened between deep permanent wrinkles. This condition is known as "cutis rhomboidalis nuchae" and is particularly to be found in those who have worked much under a bright sun; thus it is also called "sailor's skin" or "farmer's skin." The same kind of change is found on the face and backs of the hands, though here the yellowing inelastic skin may be thinned rather than thickened, and areas of telangiectasia and senile keratoses may be present.

The characteristic pathologic change is in the connective tissue below the dermal papillae. Routine histologic preparations show the connective tissue bundles to be interspersed with fibers that are narrow and fragmented and poorly stained with hematoxylin and eosin, usually being relatively basophilic. These altered fibers are strongly colored by stains which characterize elastic fibers, and it was thought for a long time that there was an increase of these fibers or a merging of degenerate elastic fibers with degenerate collagen fibers. Percival *et al.* (35) made a study of these degenerate fibers and by means of thick frozen sections showed them to be elongated and tortuous, which accounts for the appearance of short fragments seen in thinner sections. They also confirmed the observation of fat droplets in these degenerate fibers (33). With this change, which is thought to be a degeneration of collagen and not of elastica, there is usually no inflammation. The degeneration spares the uppermost papillary corium and the fibers of the deeper part of the corium are unaffected. Tunbridge *et al.* (36) examined senile skin under the electron microscope and compared the skin of covered parts with that of exposed parts. The degenerative changes that they described were virtually confined to exposed skin. Under the electron microscope the collagen fibrils can be recognized by their size and by the regular cross-banding at 640 Å intervals. In areas with senile elastosis, fibrils showing the 640 Å periods were very short, showed kinks and bends, and tended to fray and merge with amorphous material. There was a great deal of this amorphous material associated with these fibrils and there were many fibrils of the same dimensions as collagen but lacking the regular cross-striations. These were thought to be part of the degenerate collagen fibers. Material from this exposed skin was found to be abnormally susceptible to digestion by trypsin; in fact trypsin would digest away all except the regular cross-striated collagen fibrils. In normal dermis trypsin removes ground substance but not collagen, though pepsin does attack collagen. It is known that during peptic hydrolysis collagen may be modified to stain like elastic tissue (37). Tunbridge *et al.* (36) subjected normal collagen to partial hydrolysis with pepsin and produced fibrils which would stain as for elastica, and this material under the electron micro-

scope showed the merging of collagen with amorphous material and the presence of fibrils lacking the characteristic 640 Å striations. It is apparent that the main connective tissue change in senile skin is a degenerative process in collagen, very much resembling the changes that take place with partial hydrolysis of collagen. These degenerative changes in the collagen are accompanied by telangiectasia in the superficial blood vessels; there is also atrophy of the dermal papillae and flattening of the epithelium, which often shows a relative hyperkeratosis. It is in this degenerate skin that senile keratoses and carcinomata so often develop.

SENILE PURPURA

One condition that is perhaps less dependent upon exposure, and more dependent upon old age, is "senile purpura." It was described by Bateman in 1836 under the title of "purpura senilis, scurvy of old age" (38). It is a clear-cut clinical entity which seems to have been lost from many modern texts; or worse, the label has been misapplied (39). Tattersall and Seville (40) drew attention to the condition and studied in detail 60 cases which they found among 809 geriatric patients examined. The condition is not found under the age of 60, and men and women are equally affected. The incidence rises from 2 per cent in the seventh decade to 25 per cent in the tenth decade. The disease is essentially confined to the backs of the hands and dorsal aspects of the lower part of the forearms (Fig. 2). It does not extend to the fingers. Individual ecchymoses are seen in the affected area. These ecchymoses are a few centimeters in diameter, with clear-cut edges, and they fade gradually to leave a brown stain. Thus the pattern of hemorrhage is changing from week to week. The skin in this area is brittle, inelastic and transparent, and shows white scars and

FIG. 2. Senile purpura.

FIG. 3. Senile purpura. Photomicrograph, showing extreme degeneration of collagen in upper corium (stained with acid orcein).

irregular pigmentation. Tattersall and Seville compared patients with senile purpura with a control group of the same age, and found no difference in the incidence of cardiovascular and hypertensive disease. There was also no difference between the two groups as regards vitamin C excretion and the results of saturation tests; moreover, the purpuric condition was not affected by giving vitamin C. These patients had no disorder of the blood, and bleeding and clotting times and capillary resistance were normal. Fresh ecchymoses in the purpuric regions could be produced by blunt trauma, although the same trauma would produce no lesion in other sites in the same patients, nor on the backs of the hands in unaffected patients of the same age. In making a biopsy from such a lesion one is impressed with the extreme fragility of the whole skin of this area; for instance, a suture will cut out of the skin as though tearing through wet blotting paper.

Histologic sections show the epithelium and basement membrane to be normal, but there may be some atrophy of the epidermis with relative hyperkeratosis, or there may be patchy melanosis. In the subpapillary corium there is very gross degeneration of the connective tissue, which stains as does the elastic tissue (Fig. 3) already described under senile elastosis; it also shows the same digestibility with trypsin and the same electron-microscope picture. In the area of connective tissue degeneration the small blood vessels appear to have lost their connective tissue support. This shows particularly well in sections stained with the periodic-acid Schiff method (Fig. 4), which outlines the dilated, unsupported capillaries and shows a gap between their basement membranes and

FIG. 4. Senile purpura. Photomicrograph from the section shown in Figure 3. Periodic-acid Schiff stain shows up basement membranes of the blood vessel walls and lack of connective tissue support.

the dermal fibers. There is extravasation of red cells from these vessels. The total bulk of the dermis is considerably reduced in comparison with skin from this site in a younger person, but many subjects of the same age would show comparable thinning of the skin as a whole.

PRURITUS

Itching is a fairly common complaint in old people and it is unfortunate that the term "senile pruritus" is used rather indiscriminately. It is true that old people form a scratching habit rather easily; for instance, Rothman (41) describes how about half of those in a home for the aged declared that "it feels good to scratch the shins in the evening." Local factors influence the site, such as venous stasis in the lower part of the legs, and the marked tendency to asteatosis on the shins in the aged. The diagnosis of "senile pruritus" should be made only after a process of exclusion, with investigation of almost all of the causes of generalized pruritus that are considered in younger people. The common dermatoses may be found in old age, and these have been discussed by Epstein in some detail (3). Although the eczematous contact type of dermatitis is less acute than in younger groups, it may take longer to subside and may be kept active by minor irritative factors. Urticaria presents much the same problem as in younger people. Parasitic diseases should not be forgotten; scabies, in particular, is capable of spreading through an institution.

Generalized pruritus without skin lesions other than scratch marks is to be

found in some metabolic diseases. Renal failure is one cause of general itching which, however, does not occur unless there is considerable nitrogen retention. Diabetes may be associated with generalized pruritis as well as with the local perigenital type often complicated by moniliasis. The general itching in diabetes is independent of the severity of the disease, but it clears when the diabetes is properly controlled. It may be noted that the diabetic skin is dry and lacks lipid (41). The pruritus usually associated with obstructive jaundice is not caused by bile pigments in the blood, as sometimes the itching will precede the icterus by a week or two. There is evidence to suggest that the itching is related to the accumulation of bile salts in the blood.

Itching may be an early symptom of lymphoma, whether or not erythroderma be also present. Mycosis fungoides, Hodgkin's disease, lymphosarcoma and the leukemias may all on occasion have pruritis as the initial symptom, and at times it may be very severe. Rarely, too, internal carcinoma may be associated with itching (42), with or without urticaria or polymorphic eruptions. Usually in such cases the carcinoma is already extensive, but occasionally its removal has given abrupt relief of the pruritus. Drugs often cause itching eruptions, but it should be not forgotten that drug idiosyncrasy may also cause pruritis without a rash. In the presence of arteriosclerotic disease, when other causes have been excluded, the intractable itching that sometimes occurs may justifiably be regarded as a manifestation of the vascular disease. One of the most common factors in itching in old people is the asteatosis to be described in the next paragraph, and most cases of senile pruritus come under this heading. This condition, though commoner in cold weather, is distinct from the pruritus heimalis of Duhring (43), which is a rare disease and may affect young adults. In pruritus heimalis very severe itching may be reproduced by chilling the whole body in a cold bath and then warming it, but chilling of a limb does not bring on local symptoms; this suggests some factor other than local disturbance of skin (44).

Asteatosis or xerosis

This condition is not confined to old age but it is responsible for much discomfort in older people and may be considered as a common accompaniment of aging. It is usually present on the shins (Fig. 5), but may affect the skin very extensively. The slightly thickened, dry, surface keratin cracks into horny plates, between which reddish fissures develop. The condition is pruritic, is generally more troublesome in cold weather, and is greatly aggravated by washing with hot water and soap. Deficiency of the surface lipid is thought to be a factor, probably brought about by the lessened contribution of the sebaceous glands in older people, especially in cold weather, and by decreased release of lipids during cornification. In cold weather sweating is minimal and there is no emulsification of surface lipids; by a kind of paradox, the surface film may also be defective on account of lack of water. Blank has shown that keratin relies on water for its elasticity, and that dry horny material is very brittle (45). Lipid solvents not only remove natural fats and waxes from the skin

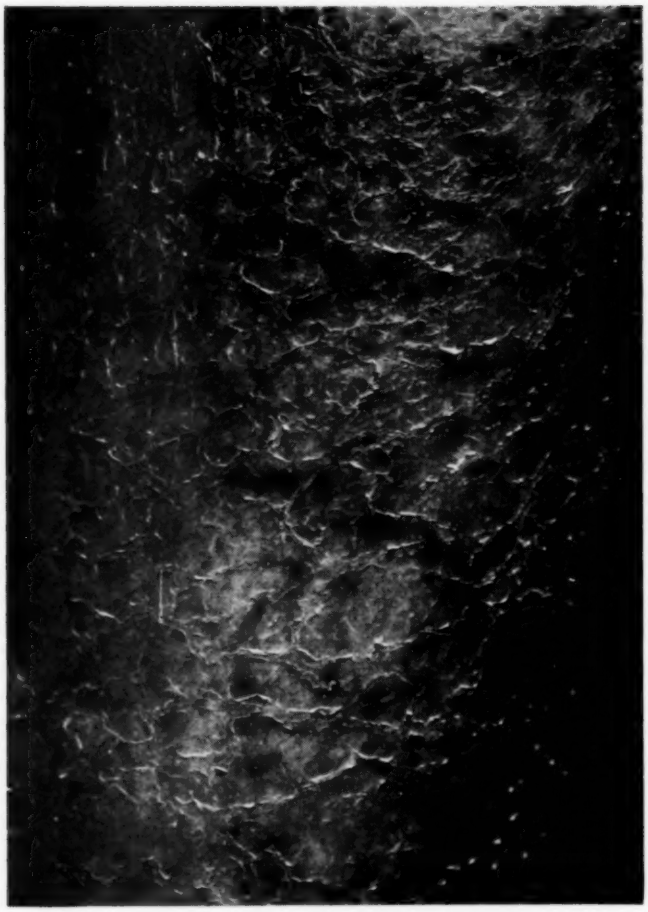

FIG. 5. Asteatosis. Detail of front of shin.

surface, but render water-extractable some important polar material belonging to the keratin. Lipid solvents or detergents, alternating with water-soaks, may be of particular importance in reducing the elasticity of the keratin. To be elastic and strong, the surface keratin must contain at least 10 per cent water, which comes mainly from the sweat or from the atmosphere; very little comes from the deeper layers of the skin, as the granular layer beneath the keratin is almost impervious (46). With low relative humidity and cold weather, the stage is set for asteastosis. Much can be achieved by reducing the damage caused by repeated use of soap and water, particularly in cold weather. Frequent application of ointments or creams is helpful, and cholesterated petrolatum (47), with or without water, is recommended.

SENILE SEBACEOUS ADENOMA

This condition is one of the less well known tumors of old skin, and it is seldom seen in younger individuals. It may be mistaken for basal-cell carcinoma. Lesions are found on the forehead or cheeks, ranging in number from one to about a dozen (Fig. 6). They are about half a centimeter in diameter and of a

FIG. 6. Senile sebaceous adenomata.

yellowish color, and usually with an umbilicated center. Histologically, the little nodules consist of circumscribed masses of enlarged sebaceous glands in the upper part of the dermis. Considering the fact that there is no formation of immature cell structures, the use of the word adenoma may be criticized. These lesions are found in old people with a greasy skin and coarse follicular openings. It is of interest that in certain areas, such as the forehead and cheeks, a true seborrhea may persist into old age, whereas sebaceous gland function over much of the body is generally thought to decline. Lobitz (48) has shown that high dosage of estrogen will temporarily suppress this type of facial seborrhea and lead to some reduction of the adenomata.

SUMMARY

1. The appearance of the aged skin of covered parts of the body is described, and changes in elasticity and in tensile strength are reviewed. Microscopically, the changes consist of shrinkage of the dermal papillae and flattening of the epithelium, and probably some alteration in the deeper collagen and elastic fibers.

2. The decrease in connective-tissue ground substance is an important factor in the diminution of hydration and turgor of the skin in old age.

3. The effects of hormones on the skin in senescence are reviewed, with special reference to the effects of sex hormones applied locally.

4. The influences of sunlight and of genetic factors on the exposed skin are discussed. The microscopic picture in senile elastosis is presented, and reference is made to the electron-microscope appearance of the degenerated fibers.

5. Senile purpura, found on the dorsal aspects of the forearms and hands, is

the result of extreme degeneration of the dermal collagen, which leads to small hemorrhages from unsupported blood vessels.

6. Some causes of pruritus in old age are considered, including asteatosis. In the maintenance of a supple horny layer, both hydration and the surface lipid film are important.

7. Senile sebaceous adenoma is discussed.

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EDITORIAL

HYPERLIPEMIA AND VENOARTERIAL LIPID DIFFERENCE

Tornblom (1) found that a male patient with essential hypertension showed higher concentration of lipids (by 165 mg. per 100 cc.) in cubital vein serum than in arterial serum. He noted that Roger and Binet in 1923 had found a higher content of lipids in blood from the right side of the heart, than from the left side, suggesting that the source of this difference might lie in some internal organ. In fact, they thought that the lungs played a part in fat metabolism similar to that of the liver in carbohydrate metabolism.

Tornblom made further observations with healthy students and obese patients. He concluded that the lipid content of venous serum almost always exceeded that of arterial serum, and that patients whose venous blood was rich in lipids usually showed a large venoarterial difference.

Since most of our studies in the field of cholesterol metabolism are made on venous blood, it is well to keep these differences in mind.

Aarseth (2) found no tendency to hypercholesterolemia among his hypertensive patients, nor did he find any correlation between arteriosclerosis and hypercholesterolemia. He did not find any increase in the incidence of obesity among patients with arteriosclerosis.

At the present time, the role of hypercholesterolemia in the etiology of arteriosclerosis seems to be a leading subject for investigation. It is well not to get too enthusiastic, since undoubtedly there are other factors at play.

MALFORD W. THEWLIS, M.D.

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